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ANGINA PECTORIS AND THE SYNDROME OF PEPTIC ULCER

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In previous communications [1] we described certain relations between the syndrome of angina pectoris and that of peptic ulcer and called attention to certain clinical patterns: 1. The symptoms of peptic ulcer and anginal symptoms may occur suddenly and simultaneously, and occasionally acute peptic ulcer may be associated with coronary thrombosis. 2. Repeated attacks of angina pectoris at rest, finally eventuating in coronary thrombosis, may occur two to three hours after meals and during the night at the hours characteristic of pain from ulcer. 3. When symptoms of angina pectoris and peptic ulcer coexist, successful treatment for symptoms of ulcer may cause remission of the anginal syndrome. 4. Epigastric localization of anginal pain may be conditioned by a preexisting peptic ulcer.

In this paper we shall attempt an explanation of these phenomena and record additional illustrative cases. The common denominator that immediately suggests itself is a simultaneous disturbance in blood flow in the coronary and in the gastric and duodenal arteries. Evidence has been adduced that the arterial architecture of the stomach and duodenum plays a role in the localization of ulcers at the sites of election. Both Reeves [2] and Jatrou [3] showed that peptic ulcers occur by preference in areas where the arterial supply is poor and where anastomoses of the marginal arterial loops are few. The role of arteriosclerosis in the genesis of some peptic ulcers in older persons is generally accepted. It seems probable that the occasional simultaneous occurrence of coronary thrombosis and acute or penetrating peptic ulcers can be explained by simultaneous arterial occlusions in both territories, induced by the same systemic causes. Or else shock resulting from closure of an artery in one area may induce secondary thrombosis in the other one. Cases 1 and 2 fall into this category. But this mechanism is rarely operative.

During the past twenty-five years the understanding of coronary arteriosclerosis and its role in the causation of the anginal syndrome and of myocardial necrosis has been greatly clarified. Investigators have learned that anginal pain is caused by myocardial anoxemia due to insufficient flow of blood through the coronary arteries. They have been so impressed by the pathologic changes in the

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1. Boas, E. P., and Levy, H.: Angina Pectoris and the Peptic Ulcer Syndrome, J. Mt. Sinai Hosp. **8**:422, 1942. Boas, E. P., in discussion on Walsh, B. J.; Bland, E. F.; Taquini, A. C., and White, P. D.: The Association of Gall Bladder Disease and of Peptic Ulcer with Coronary Disease: A Post-Mortem Study, Am. Heart J. **21**:697, 1941.

2. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, Surg., Gynec. & Obst. **30**:374, 1920.

3. Jatrou, S.: Ueber die arterielle Versorgung des Magens und ihre Beziehung zum Ulcus ventriculi, Deutsche Ztschr. f. Chir. **159**:196, 1920.

coronary arteries that they have paid little attention to the functional changes in the coronary circulation that may also give rise to anoxemia of the heart muscle. In recent years it has been shown that myocardial infarction may result from transient coronary insufficiency in a patient with diseased coronary arteries. This insufficiency may be due to hemorrhage, shock or any physical strain that leads to an imbalance between the oxygen needs of the heart muscle and the capacity of the diseased coronary arterial bed to deliver to the heart muscle sufficient oxygen-carrying blood.

There is as yet little recognition of the role of reflex coronary vasoconstrictor factors in the genesis of the anginal syndrome and of myocardial infarction. Heberden,[4] in his original description of angina pectoris, called it a spasmodic complaint, and pointed out that "its attacks are often after the first sleep, which is a circumstance common to many spasmodic disorders." Roberts [5] emphasized the importance of psychogenic and neurogenic factors in the production of the anginal syndrome. More recently one of us [6] called attention to reflex mechanisms in certain coronary syndromes.

The significance of vasomotor changes of the caliber of the coronary arteries in the clinical syndromes of coronary artery disease has been reviewed by Gilbert.[7] Vasconstrictor impulses reach the coronary arteries through the vagus nerve. Dietrich and Schweigel [8] in von Bergmann's laboratory found that distention of the stomach with a rubber balloon caused a marked decrease in coronary flow. This effect was abolished by section of the vagus nerve or by administration of atropine. These experiments were confirmed by Gilbert, Fenn and LeRoy.[9] Distention of the dog's stomach at the esophageal orifice has the greatest effect in reducing coronary flow. This observation may throw some light on the common association between hiatal hernia and angina pectoris. Gilbert, in a roentgen study of 44 patients with angina pectoris, discovered hiatal hernia in 17 per cent. These experiments also offer an explanation for the occurrence of angina pectoris with diverticula of the lower part of the esophagus and for angina pectoris induced by swallowing.[10] Swalm and Morrison [11] recorded cases in which distention of the esophagus caused anginal pain and changes in the RT segment of the electrocardiogram as well as extrasystoles.

Manning, Hall and Banting [12] carried out prolonged electrical stimulation of the vagus nerve in dogs. At autopsy they repeatedly found capillary congestion and hemorrhage in the heart, some early hyaline degeneration in the cardiac muscle and infarcted areas in the anterior papillary muscle. Changes in the form of the T wave were constant. In addition, there was marked congestion with hemor-

4. Heberden, W.: Commentaries on the History and Cure of Diseases, Boston, Wells & Lilly, 1818, p. 296.

5. Roberts, S. R.: Nervous and Mental Influences in Angina Pectoris, Am. Heart J. **7**:21, 1931.

6. Boas, E. P.: Some Immediate Causes of Cardiac Infarction, Am. Heart J. **23**:1, 1942.

7. Gilbert, N. C.: Influence of Extrinsic Factors on the Coronary Flow and Clinical Course of Heart Disease, Bull. New York Acad. Med. **18**:83, 1942.

8. von Bergmann, G.: Das "epiphrenale Syndrom," seine Beziehung zur Angina pectoris und zum Kardiospasmus, Deutsche med. Wchnschr. **58**:605, 1932.

9. Gilbert, N. C.; Fenn, G. K., and Le Roy, G. V.: The Effect of Distention of Abdominal Viscera on Coronary Blood Flow and Angina Pectoris, J. A. M. A. **115**:1962 (Dec. 7) 1940.

10. Edeiken, J.: Angina Pectoris and Spasm of the Cardia with Pain of Anginal Distribution on Swallowing, J. A. M. A. **112**:2273 (June 3) 1939.

11. Swalm, W. A., and Morrison, L. M.: Relation of Gastro-Intestinal Disorders to Angina Pectoris and Other Acute Cardiac Conditions, Rev. Gastroenterol. **6**:41, 1939.

12. Manning, F. W.; Hall, G. E., and Banting, F. G.: Vagus Stimulation and the Production of Myocardial Damage, Canad. M. A. J. **37**:314, 1937.

rhage in the stomach and duodenum, particularly in the region of the pylorus. When the vagal action was augmented by administration of physostigmine, all of the lesions were more marked, and actual ulcers were found in the pylorus. Hall, Ettinger and Banting [13] produced lesions of the myocardium and of the coronary arteries by long-continued daily administration of acetylcholine (activator of the vagus nerve) to dogs.

Several observers have reported that patients with disease of the coronary arteries exhibit cardiac slowing from pressure on the carotid sinus more frequently and to a greater degree than do normal persons.[14] This suggests increased sensitivity of the vagus nerve.

Hochrein and Schleicher [15] called attention to the association of peptic ulcer and angina pectoris and suggested that underlying many symptoms in both conditions, as well as their concurrence, is an altered tonus of the vegetative nervous system, particularly vagotonia.

Von Bergmann [16] and his school, and many others, have stressed the importance of disturbances of the vegetative nervous system in the etiology and the symptomatology of peptic ulcer and have pointed out that functional disturbances of the gastrointestinal tract may induce the same symptoms as do true ulcers. Indeed, they have expressed the belief that one cannot draw a sharp line of demarcation between the organic lesions and the functional disturbances. The syndrome of peptic ulcer is often encountered without roentgen evidence of gastrointestinal ulceration, and many patients with disease of the coronary arteries and with symptoms of peptic ulcer have no ulcer demonstrable on roentgen examination. Kaufmann [17] suggested that the periodicity of symptoms and clinical manifestations in patients with ulcer are due to periodic changes in activity of the vagus nerve.

The syndromes of peptic ulcer and angina pectoris have many similarities. Both conditions affect males predominantly, and both have a definite familial distribution. Angina pectoris, as well as peptic ulcer, is rarely encountered in Negroes.[18] More significant, probably, is the periodicity of symptoms in both conditions, the alternation of states of activity and remission. Periodicity of symptoms is well recognized in the syndrome of peptic ulcer and is indeed of great diagnostic value. It is not widely recognized that the anginal syndrome frequently exhibits similar alterations of activity and freedom from pain. Anginal symptoms may reappear suddenly after the patient has been without pain for months or years. Sometimes this is due to fresh arterial and myocardial lesions; at times anginal pain may recur on effort without evident development of fresh lesions and with no recognizable cause. In both disease states the symptoms tend to recur during periods of emotional stress.

Angina pectoris, like the pain from peptic ulcer, frequently awakens the patient from sleep during the night. During sleep there is increased activity of the vagus

13. Hall, G. E.; Ettinger, G. H., and Banting, F. G.: An Experimental Production of Coronary Thrombosis and Myocardial Failure, Canad. M. A. J. **34**:9, 1936.

14. Braun, L., and Samet, B.: Zur klinische Bedeutung des "Vagusdruckes," Wien. klin. Wchnschr. **40**:1383, 1927. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**:297, 1933. Mandlestamm, M. E.: Vegetative Cardiac Reflexes and Angina Pectoris, Vrach. gaz. **35**:741, 1931.

15. Hochrein, M., and Schleicher, I.: Ulcus pepticum und Angina pectoris, München. med. Wchnschr. **88**:328, 1941.

16. von Bergmann, G.: Ulcus Pepticum, in von Bergmann, G.; Staehelin, R., and Salle, V.: Handbuch der inneren Medizin, ed. 3, Berlin, Julius Springer, vol. 3, pt. 1, p. 524.

17. Kaufmann, J.: Bemerkungen über die pathologische Bedeutung der Funktionsstörungen des Magens, Arch. f. Verdauungskr. (supp.) **19**:85, 1913.

18. Boland, F. K.: Peptic Ulcer and Diseases of Biliary Tract in Southern Negro: Influence of Diet, Ann. Surg. **102**:724, 1935.

nerve. Carlson [19] noted that hunger contractions of the stomach are often more vigorous during sleep, presumably because of relative overactivity of the vagus nerve in consequence of the elimination of all inhibitory influences that pass over the splanchnic nerves; Schmidt [20] attributed the frequent occurrence of visceral colic during sleep to overactivity of the vagus nerve. Klewitz [21] and Messerle [22] observed prolongation of the PR interval during sleep. Boas and Goldschmidt [23] described marked reduction of heart rate together with development of pronounced sinus arrythmia during sleep. All these are evidences of increased vagal activity.

In 1939 Weinstein and Mattikow [24] reported 2 cases in which anginal attacks developed before meals and in which the appearance of angina was associated with hypoglycemia. Administration of dextrose promptly relieved the anginal seizures. One of the patients had severe angina on walking before meals and could exert himself more readily after having eaten. Both patients were treated with low carbohydrate, high protein diets and were relieved of their anginal pain. Sandler [25] presented evidence to show that sudden spontaneous lowering of blood sugar may induce anginal attacks and that patients may be relieved of their spontaneous anginal attacks by diets that combat great fluctuation of blood sugar levels. It is known that overdosage with insulin may induce anginal pain and electrocardiographic changes. Peskin [26] reported the cases of patients with recurrent abdominal pain simulating peptic ulcer and associated with relative hypoglycemia, whose pains were relieved by diets low in carbohydrate.

Himwich and his associates [27] showed that acute hypoglycemia in dogs gives rise to a picture of widespread autonomic stimulation with initial preponderance of sympathetic activity and subsequent evidence of parasympathetic activity. Vagal effects noted were progressive slowing of the heart and prolongation of the PR interval. After section of the vagus nerve, these phenomena did not appear. Other authors [28] have described an increase of gastric motility and of secretion resulting from hypoglycemia induced by large doses of insulin.

Bender and Siegal [29] showed that acetylcholine or some similar agent is released in the body in response to hypoglycemia induced with insulin. We have examined the blood sugar levels in a number of patients with the combined syndromes of ulcer and anginal pain but have discovered no hypoglycemia. However, it seems probable that this mechanism may be active in some of the cases.

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19. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916, vol. 7, p. 150.

20. Schmidt, R.: Die Schmerzphänomene bei inneren Krankheiten, ihre Pathogenese und Differential Diagnose, ed. 2, Leipzig, W. Grau-Müller, 1910, p. 62.

21. Klewitz, F.: Der Mechanismus der Herzreaktion im Schlafe, Deutsches Arch. f. klin. Med. **101**:267, 1919.

22. Messerle, N.: Ueber den Einfluss des extrakardialen vegetativen Nervensystems auf das Elektrokardiogram, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:499, 1928.

23. Boas, E. P., and Goldschmidt, E. F.: The Heart Rate, Springfield, Ill., Charles C Thomas, Publisher, 1932, p. 81.

24. Weinstein, J., and Mattikow, B.: Angina Pectoris as a Predominating Symptom in Spontaneous Hypoglycemia, Ann. Int. Med. **12**:1886, 1939.

25. Sandler, B. P.: The Control of the Anginal Syndrome with a Low Carbohydrate Diet, M. Ann. District of Columbia **10**:371, 1941.

26. Peskin, A. R.: Hypoglycemia with Paradoxical Sugar Tolerance Curve Simulating Peptic Ulcer, J. A. M. A. **108**:1601 (May 8) 1937.

27. Himwich, H. E.; Martin, S. J.; Alexander, G. A. D., and Fazekas, J. F.: Electrocardiographic Changes During Hypoglycemia and Anoxemia, Endocrinology **24**:536, 1939.

28. Fortuyn, J. D.: Hypoglycemia and the Autonomic Nervous System, J. Nerv. & Ment. Dis. **93**:1, 1940.

29. Bender, M. P., and Siegal, S.: Release of Autonomic Humeral Substances in Hypoglycemic Cats and Monkeys, Am. J. Physiol. **128**:324, 1940.

The histories presented in this paper, interpreted in the light of the foregoing discussion, suggest that the common denominator of the syndromes of angina pectoris and peptic ulcer is heightened excitability of the vagus nerve. Symptoms of peptic ulcer may arise from vagal activity in the stomach, and symptoms of angina pectoris may result from vagal coronary vasoconstriction. A functional disturbance of one organ may reflexly, via the vagus nerve, induce a disorder in the other. This train of events is illustrated in case 3, in which angina pectoris appeared with recurrence of a gastric ulcer, and in cases 6 and 7 with "ulcer timing" of the anginal seizures. More often a constitutionally determined heightening of tone or excitability in the vagus nerve seems to be responsible for simultaneous dysfunction of both the stomach and the heart. Cases 1, 2 and 5 illustrate this condition. Some day investigation may disclose what role, if any, the acetylcholine mechanism plays in these states of heightened activity of the vagus nerve.

Patients with angina pectoris, as a rule, walk with greater difficulty after eating because anginal pain is more readily induced. It is caused by the increased work imposed on the heart by the digestive process as well as by the reflex coronary constriction resulting from gastric distention and contraction. Gilbert, Fenn and LeRoy [9] succeeded in abolishing or lessening this greater susceptibility to anginal pain after eating by giving atropine. Some patients with the combined syndromes of peptic ulcer and angina pectoris walk more freely and farther after a meal (case 4). In these patients anginal pain developing on effort is a product of the various forces operative at the moment. Whether the patient can walk more freely when the stomach is full or when it is empty will depend on which influence is the stronger, the vasoconstrictor effect on the coronary arteries, conditioned reflexly by the gastric distention induced by the meal, or the inhibition of the hunger contractions by the introduction of food into the stomach and the consequent reduction of afferent impulses or of vagal tone.

Patients with the combined syndromes of peptic ulcer and angina pectoris when treated for the symptoms of peptic ulcer often report relief from the anginal seizures. Such patients should receive a modified Sippy diet or some other suitable diet, with frequent feedings. In addition they should receive full doses of atropine, enough to induce dryness of the mouth; this necessitates giving from $\frac{1}{150}$ to $\frac{1}{75}$ grain (0.43 to 0.86 mg.) three or four times a day. One-third to $\frac{1}{2}$ grain (0.022 to 0.032 Gm.) of phenobarbital given three times a day lessens reflex excitability. In some cases alkalis or colloidal aluminum hydroxide may be useful; in others these drugs seem to be of less value.

Glyceryl trinitrate should be used freely for postprandial pain, no matter where the pain is located. At times erythrol tetranitrate, $\frac{1}{2}$ to 1 grain (0.032 to 0.06 Gm.) given four times a day, is helpful. Theophylline with ethylene diamine in our experience gives no relief and may aggravate symptoms by irritating the stomach.

The rigidity with which this regimen should be carried out and the duration of treatment vary from case to case. In the presence of a peptic ulcer or of symptoms suggesting advanced coronary narrowing and imminent coronary occlusion treatment must be prolonged. If it is suspected that coronary closure is occurring—and this can be judged only by the frequency of the pain and the readiness with which it comes on—the patient should be put to bed and treated as though he had coronary thrombosis. Sudden change in the provoking causes of anginal pain, with change from angina pectoris after effort to anginal attacks at rest, indicates a progressive lesion in the coronary arteries and heralds the development of cardiac infarction. Rest, the use of vasodilators and an ulcer regimen may relieve the coronary insufficiency in these cases and allow the establishment of sufficient collateral circulation to enable the patient to survive the closure of the

particular coronary artery whose progressive closure is at the root of the exacerbation of symptoms.

Patients who have had peptic ulcer and who subsequently have disease of the coronary arteries may experience anginal pain on effort or the pain of coronary thrombosis only in the abdomen (patients in cases 9 to 13). In some cases the pain may start in the abdomen and radiate to the chest or the arms; in others it may commence in the chest and radiate to the abdomen. This distribution of pain may be due to reflexes initiated by the disturbance in the heart or, as we suggested in a previous paper,[30] the pain may simply travel along nerve pathways previously sensitized by the ulcer.

SUMMARY

Certain relations between the syndromes of angina pectoris and peptic ulcer are described. It is suggested that neurogenic mechanisms mediated by the vagus nerve are concerned in this association.

REPORT OF CASES

Sudden Occurrence or Recurrence of Peptic Ulcer with Symptoms; Simultaneous Onset of Angina Pectoris with Electrocardiographic Evidence of Myocardial Damage.

CASE 1.—A man, F. G., had meningitis at the age of 32. At the age of 47 a roentgenogram showed a penetrating peptic ulcer. The symptoms of ulcer persisted for some three years and then abated. At the age of 51, for a period of two months he was awakened regularly at 2 a. m. by a burning pain in the right lower region of the chest, radiating to the middorsal part of the spinal column, which was relieved by taking alkaline powders. During this same period he experienced similar pain when walking in the cold.

The following year, at the age of 52, he had a recurrence for two months of similar nocturnal pain which lasted two or more hours at a time. These attacks were not relieved by the powders. During this time he was unable to walk more than three blocks because, regardless of the weather, he would experience pain in the lower substernal area and in the right lower region of the chest, compelling him to stop.

He was a thin man. There was no tenderness in the epigastrium. Fluoroscopic study revealed a heart normal in size and configuration. There was a systolic murmur at the apex. The blood pressure was 170 systolic and 100 diastolic. The electrocardiogram was normal.

He was referred to the Mount Sinai Hospital. There the hemoglobin content was found to be 95 per cent and the white blood cell count 9,300. The stool was negative to the guaiac test. A roentgen film showed a shallow pocket in the posterior wall of the stomach, high up on the lesser curvature. There was an incisura at the antrum. Gastroscopic inspection showed a small cleancut shallow ulcer about midway up on the lesser curvature. Subsequent roentgen examination revealed diminution in the size of the ulcer pocket. An electrocardiogram taken two weeks after the normal record obtained in the office showed partial inversion of the T wave in lead IV.

An ulcer diet and alkalis induced complete subsidence of his symptoms.

The following year, at the age of 53, he was readmitted to the hospital, complaining of intermittent claudication in both legs. At this time he mentioned no symptoms of ulcer or anginal symptoms but said that he had recently had pain in the right lower quadrant of the abdomen and diarrhea. A gastrointestinal roentgenogram taken at this time showed no abnormality. The spleen was felt 2 fingerbreadths below the costal margin. An electrocardiogram showed a diphasic, partially inverted T wave in lead IV.

The striking point in case 1 is the electrocardiographic change developing during a period of recurrence of the symptoms of ulcer and of coronary disease. The symptoms of peptic ulcer were the most striking, and differed from the symptoms of ulcer which the patient had described in previous years. First, the attacks in general were of longer duration—in fact, one attack lasted as long as five hours; second, for the first time the pains were not relieved by alkali, and, third, these symptoms of ulcer were associated with symptoms of angina on effort.

30. Boas, E. P., and Levy, H.: Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris with Special Reference to Shoulder Pain, Am. Heart J. **14**:541, 1937.

CASE 2.—This instance was reported in detail elsewhere [30] as the case of a man who at the age of 49 had a sudden onset of pain suggesting ulcer, as well as of anginal pain, in whom electrocardiography revealed an infarct of the anterior aspect of the left ventricle and roentgen examination disclosed a penetrating gastric ulcer of the reentrant angle.

In both cases 1 and 2 organic lesions of the heart and the stomach developed simultaneously. Brooks [31] described a case in which the diagnosis of coronary thrombosis was made and in which a perforated peptic ulcer was suspected. At autopsy both acute coronary thrombosis and a perforated duodenal ulcer were found.

Angina Pectoris with Recurrence of Gastric Ulcer.

CASE 3.—A man, B. L., at the age of 38 complained for several months of epigastric pain radiating through to the back, occurring one hour after meals. Roentgen study disclosed a gastric ulcer. The symptoms remitted for over eight years but recurred when the patient was 46 years old. The pain was similar, occurring in the epigastrium about one hour after meals. He then, for the first time, noted a squeezing pain in the anterior part of the chest, which radiated to the epigastrium, occurring one hour after meals and lasting about one to two hours at a time. He walked less readily than previously. After 3 blocks he would become fatigued and would then experience midchest pain radiating straight through to the back, compelling him to rest, which led to relief.

Physical examination at this time disclosed a well built man. The lungs were clear; some epigastric tenderness was present. Fluoroscopic study revealed a heart of normal size and configuration; the heart sounds were of good quality. The blood pressure was 190 systolic and 110 diastolic. The electrocardiogram showed no significant abnormalities.

The next year, at the age of 47, he had a recurrence of his symptoms of ulcer, and roentgen examination again showed a gastric ulcer. He was given an appropriate diet and remained well until the next year, when he complained of pain in the right lower region of the chest, occurring at irregular intervals. This pain was unrelated to meals or effort, but after walking quickly on an upgrade he would become fatigued and would be compelled to rest for several minutes. There was no recurrence of the epigastric midchest pain on walking.

Physical examination including electrocardiographic study showed little change. The blood pressure was somewhat lower, 150 systolic and 90 diastolic.

Increased Capacity for Walking After Meals.

CASE 4.—A man aged 54 had suffered for over twenty years from heartburn in the lower substernal area, occurring one to two hours after meals and relieved by alkali. The pain would remit for several years at a time. No gastrointestinal roentgenograms were taken.

At the age of 50 he experienced a sudden attack of palpitation associated with very slight midsternal pain several hours after breakfast, while being shaved. There was no breathlessness. One hour later the sinus rhythm was regular, the heart rate was 80 beats per minute, the blood pressure was 138 systolic and 90 diastolic, the heart sounds were dull and there were no murmurs. An electrocardiogram taken on the following day showed a PR interval measuring 0.22 second and moderate lowering of the T waves in all leads.

During the next four years he continued at his work and felt quite well; he was able to walk freely at all times. At the age of 54 he began to experience pain in the left lower region of the chest and in the lower substernal area, occurring intermittently, chiefly three to four hours after meals, and relieved by food. One week after the onset of these symptoms, while walking he experienced epigastric pain radiating to the lower part of the chest and compelling him to rest. He was then given a Sippy diet with a powder. Epigastric pain on walking continued for three weeks, when weakness and very slight pain in the lower midchest region replaced the epigastric pain on walking. The pain in the chest was relieved by a short rest. During this time, embracing both phases of epigastric and thoracic pain on walking, he noted that he could walk more freely and greater distances on a full stomach. After he had been on the diet for five weeks, all his symptoms remitted, and he was examined two weeks later. The findings on general physical examination were unchanged, but an electrocardiogram taken at this time exhibited normal voltage of the T wave in leads I and II.

The foregoing history, in addition to pointing out the increased capacity for walking after meals, also illustrates the clinical appearance of previously silent

31. Brooks, H.: Abdominal Signs and Symptoms of Thoracic Disease, Rev. Gastroenterol. 3:143, 1936.

coronary disease, brought to light by recurrent symptoms of peptic ulcer. It shows too the remission of the anginal syndrome as the pain of peptic ulcer was relieved by medication and diet.

Recurrence of Angina Pectoris with Onset of Symptoms of Peptic Ulcer; Delayed Development of Duodenal Ulcer.

CASE 5.—A man, A. B., gave no history of previous abdominal symptoms. Nine months before he came for examination, at the age of 45, as he left his home one morning and started walking, he was seized by pressure in the lower part of the chest, reflected into both upper extremities, compelling him to halt. This anginal pain occurring only during the morning walk continued for four weeks. The pain then remitted completely for eight months, and during this time he felt entirely well. Then, two weeks before he came for examination, immediately after his usual noonday meal, he became dizzy and pale, and vomited. That evening epigastric pain without radiation was experienced. It lasted for some two hours and finally was relieved by magnesium hydroxide. Following this episode the epigastric pain recurred mornings at 11:30; it would then be relieved by taking lunch and would recur at 3:30 in the afternoon, beginning in the epigastrium, radiating to the lower part of the chest and lasting fifteen minutes. He would desist from his work for a few minutes and find relief. Three days before he was examined, at 9 a. m., one hour after breakfast, he experienced midabdominal pain, reflected to the lower part of the chest and lasting two hours. That night just before retiring, at midnight, he had severe midabdominal pain radiating to the lower part of the chest, where it was more intense, for a half hour. The following day three attacks were experienced, at 12 noon, at 4 p. m. and at midnight, each one lasting about twenty minutes. He complained of no pain in the chest on walking at this time.

He was a well built man of good color; the lungs were clear; there were no abdominal findings. Fluoroscopic inspection revealed a heart normal in size and configuration. The heart sounds were of good quality; there were no murmurs. The blood pressure was 130 systolic and 80 diastolic. The electrocardiogram was normal. It appeared clinically that the patient was suffering from angina pectoris and possibly peptic ulcer. He was given a modified Sippy diet and an alkali to take between meals. A gastrointestinal roentgenogram taken immediately after the examination showed no peptic ulcer. Thereafter he continued to experience diffuse pain in the upper abdominal region on the right and left sides, reflected to the upper dorsal region of the spinal column, chiefly at 9 p. m., three hours after dinner. Glyceryl trinitrate, while not immediately effective, reduced the duration of this pain from the usual thirty minutes to five minutes. At one time he had similar pain at 4 p. m., quickly relieved by this drug. The electrocardiogram taken six weeks after the first one showed no change.

Seven months later he had recurrent pain in the left hypochondrium, radiating to the lower part of the epigastrium, always at 10 a. m, two hours after breakfast, and at 4 p. m., four hours after lunch. At this time, walking 5 blocks would provoke pain in the left forearm with slight heaviness in the lower midthoracic region. Examination again showed no change in the electrocardiographic tracing. At Mount Sinai Hospital a barium sulfate meal showed a persistent deformity involving the distal third of the duodenal bulb. This was interpreted as the result of ulceration. There was also evidence of an irregular shadow encroaching on the magenblase in the region of the greater curvature. There was a 30 per cent residue in the stomach after six hours. Gastroscopic inspection failed to visualize any lesion in the esophagus or in the stomach. The Rehfuss test meal showed, during fasting, free acidity of 64, with total acidity of 75. With a soft diet, milk and cream, and medication with aluminum hydroxide, the symptoms gradually disappeared.

In case 5 the symptoms of peptic ulcer came on suddenly, with great severity, and were accompanied by symptoms of angina pectoris. Roentgen study, however, revealed no ulcer at the onset. We do not know how long it took for the ulcer to develop, but it was certainly a matter of weeks. The lesion was discovered at the first roentgen examination seven months later. The course of events here is analogous to that observed in patients with prodromal symptoms of coronary thrombosis, in whom anginal attacks may persist for weeks before there is objective evidence of coronary closure. Similarly, symptoms of peptic ulcer may come on suddenly with no roentgen evidence of ulceration. Only after a period of weeks may the ulcer be revealed by the roentgen rays.

Repeated Anginal Attacks Occurring at Rest and Giving Warning of Impending Coronary Closure, Commonly Occurring One or Two Hours After Meals or at Night and Simulating Peptic Ulcer in Their Timing and in the Location and Character of the Pain.

CASE 6.—I. S., a printer aged 43, was ill for ten weeks with fever and pain and swellings of joints. He had never experienced symptoms suggesting peptic ulcer. At the age of 50 he first noted heart burn, situated high in the epigastrium and radiating to the throat, occurring one to two hours after meals and lasting a few minutes. For six weeks these symptoms persisted, with remissions of a few days at a time. Then, one morning, heart burn again was felt at exactly the same hour. This time, however, it radiated to both shoulders and to the head and the neck, and lasted throughout the day, relieved but slightly by food. Following this prolonged attack, heart burn was regularly provoked by walking 5 or 6 blocks but did not compel him to rest. He continued at his work and was examined two weeks after the prolonged attack of heart burn.

He was a well built man of sallow complexion. The lungs were clear. There was no abdominal tenderness. Fluoroscopic study revealed a heart of normal size and configuration. The first heart sound was somewhat dull; a systolic murmur was audible at the apex. The blood pressure was 120 systolic and 75 diastolic. The electrocardiogram revealed Q waves and negative T waves in leads II and III. There was slight elevation of the RT segment in both these leads, indicating that the lesion was a recent one.

It is clear that this patient suffered coronary thrombosis two weeks previously and that the ulcer-like symptoms beginning six weeks before that were in the nature of premonitory symptoms. Do these represent repeated spasms of the coronary arteries leading finally to thrombosis? There is no evidence of an acute peptic ulcer or even of an ancient ulcer.

CASE 7.—M. S., a man aged 56, had had hay fever for several years. The symptoms of hay fever set in on Aug. 16, 1940. Three days later he was drenched in a rainstorm. The next morning he was loath to leave his bed and noted midsternal pain. During this day he suffered four or five attacks of pain in the middle of the substernal area, radiating to the left upper extremity, each attack lasting approximately ten minutes. He took to bed and for the next week experienced repeated attacks; the last one, two days before examination, was the most intense and lasted fifteen minutes. He had never experienced pain in the chest on walking.

Examination on August 29 revealed a well built man. The pupils reacted normally to light. The lungs were clear. Fluoroscopic study revealed a heart of normal size and configuration. The heart sounds were of good quality; there were no murmurs. The blood pressure was 160 systolic and 80 diastolic. The electrocardiogram showed a shallow diphasic T wave in lead I and a sharply inverted T wave in lead IV, evidences of a recent infarction of the anterior aspect of the left ventricle.

He remained in bed for two months, experiencing recurrent attacks, some severe enough to require morphine by hypodermic injection. Subsequently he noted that moderate effort, such as walking 3 blocks slowly, would provoke breathlessness and pain in the lower midthoracic region, compelling him to rest. When next seen, in June 1941, he stated that for the preceding four weeks he had suffered epigastric pain two hours after meals and that at 3 a. m. on the day of his visit he had been awakened by the same epigastric pain. He stated that he had never experienced such postprandial epigastric symptoms in the past. In view of the postprandial timing of the recent symptoms, the initial history was reviewed. When asked to enlarge on his original statement of "four or five attacks" of midsubsternal pain on the first day symptoms occurred, he remarked that attacks occurred at 4 a. m., 10 a. m., 3 p. m. and again at 3 a. m. (He had his breakfast at 8 a. m., lunch at noon, dinner at 6 p. m. and took no late supper.) During the following week the attacks referred to occurred at 3 a. m., awakening him from sleep.

Physical examination in June 1941 disclosed good heart sounds. The blood pressure was 161 systolic and 90 diastolic. The electrocardiogram showed a normal upright T wave in lead I and a diphasic T wave in lead IV.

In case 7 the periodicity of the initial symptoms, occurring during the phase of gradual coronary closure, was not recognized until the characteristic periodicity of symptoms occurring nine months later led to a review of the original symptomatology.

CASE 8.—I. K., a man aged 58, had known of some degree of hypertension for one year. For eight years he had complained of pain in his calves on walking a few blocks, compelling him to slow his pace. He had not suffered from digestive symptoms in the past. At no time did he experience pain in the chest while walking. If he quickened his pace, pain in the calves was felt. Beginning about six weeks before he came for examination and occurring about every other day, attacks of severe midthoracic pain were experienced chiefly at 3 to 4 p. m. as well as in the hours between midnight and 4 a. m. The pain would radiate to the gums, then to the upper dorsal area and to both upper extremities. The attacks of pain lasted one or two hours and were associated with slight chilliness, but there was no perspiration, dizziness, nausea, vomiting or abdominal pain. During the bouts of pain he had no desire for food. On several occasions sodium bicarbonate afforded relief from the pain by inducing belching. The most severe attack, occurring three days before examination, awakened him from sleep at 4 a. m., and the pain persisted for more than two hours. The relief afforded by sodium bicarbonate was transient, lasting but five minutes.

He was a well built man, weighing 147 pounds (66.5 Kg.). There was no abdominal tenderness. Inconstant rales were heard at the bases of both lungs. Fluoroscopic study revealed moderate enlargement of the left ventricle, slight enlargement of the left auricle and moderate general dilatation of the aorta. The first heart sound was dull. A systolic murmur was heard at the apex. The blood pressure measured 130 systolic and 75 diastolic. The electrocardiogram showed slurring of the QRS complex in all leads and large Q waves and diphasic T waves in leads I and IV. The temperature was 98 F. by mouth. The sedimentation rate of the red blood cells was 18 mm. in seventy minutes.

The patient in case 8 had prodromal symptoms of coronary occlusion for six weeks before the closure finally took place. It is unlikely that postprandial anginal pain is caused solely by the increased work of the heart provoked by digestion. Anginal pain may appear while the patient is still eating, or else during the night after digestion is completed. The immediate cessation of postprandial pain so commonly achieved by the eructation of gas also speaks for a neurogenic reflex mechanism.

Abdominal Localization of Anginal Pain in Patients with Antecedent Peptic Ulcer.

CASE 9.—A man, M. J. C., in 1934, at the age of 35, complained for several months of hunger pains in the upper part of the abdomen, occurring three to four hours after meals and relieved by food. Two years later gastrointestinal fluoroscopic examination apparently showed no ulcer. At this time he complained of right-sided abdominal pain, which was subsequently diagnosed as renal calculus. The right kidney was removed for calculi in 1936. In November 1940, while running to catch a street car, he suddenly experienced a sharp pain high up in the epigastrium. The pain lasted about half a minute and did not radiate. Two days later he noted, for the first time, similar nonradiating epigastric pain on walking a few blocks, particularly marked shortly after meals. He would be compelled to rest. Late in November the epigastric pain recurred, became progressively worse and radiated to the left lower part of the chest and to the left upper extremity, and lasted about twenty-four hours. Subsequently the temperature was elevated to 103 F.

We first saw him six days after this attack. The lungs were clear; the heart was not enlarged to percussion, and the heart sounds were dull; there was no hepatic congestion. Several weeks later fluoroscopic study showed slight enlargement of the left ventricle. The electrocardiogram showed low voltage, with slurring of the QRS in all leads. The T wave in lead I was inverted. In lead IV there was a large Q wave and a deep inverted T wave.

The patient in case 9 had had symptoms of peptic ulcer at the age of 35. When he was 51 years old, anginal pain developed on effort, which was experienced in the epigastrium. During the subsequent coronary thrombosis the initial pain was epigastric but radiated to the precordium and the left arm.

CASE 10.—A man, I. A., at the age of 25, first noted heart burn in the lower substernal area one-half hour after meals. It was relieved by taking some alkali. The attacks persisted for over twenty years without remission, and during this time he never experienced pain in the abdomen. At the age of 46, for the first time, he experienced nocturnal heart burn, which was relieved by alkali. Roentgen examination was first done at the age of 47 and revealed an irregular duodenal cap, which was diagnosed as a duodenal ulcer. The symptoms were controlled by an appropriate diet. At the age of 49, shortly after eating some cake he suffered

heart burn. Cake had often provoked similar heart burn. Water gave him temporary relief; but one hour later, the heart burn was followed by cramps in the lower substernal and right hypochondriac regions, which lasted until he took sodium bicarbonate, about ten minutes. He slept that night, suffering no nocturnal pain, and the next day returned to work. Beginning immediately after the attack, in fact the same evening, as he left his car and began to walk, he noted pain in the lower substernal region, radiating upward under the sternum and compelling him to slow his pace. Some relief was afforded by belching. On walking this symptom persisted.

Physical examination three weeks after this attack revealed a stocky man whose lungs were clear and who had no abnormal abdominal findings. Fluoroscopic study revealed some enlargement of the left ventricle. The heart sounds were dull. A musical systolic murmur was heard over the entire precordium. The blood pressure was 140 systolic and 80 diastolic. The electrocardiogram showed no abnormality except for slight slurring of the QRS.

In case 10 the acute onset of angina pectoris followed the pattern of the previous pain, from ulcer, and therefore masqueraded as a recurrence of that lesion.

Case 11.—A man, S. G., complained of pain low in the epigastrium, beginning at the age of 26 and recurring intermittently for twenty-five years. It occurred three hours after meals and often awakened him at 2 a. m. Roentgen examination at the age of 50 revealed a peptic ulcer. On a diet the pain remitted, and he remained without symptoms of ulcer thereafter. At the age of 58 he first complained of pain in the calves on walking a few blocks, compelling him to halt. Despite the marked reduction in the number of cigarets which he smoked, these symptoms remained unaltered. At the age of 63, while on a short walk one morning, before breakfast, he experienced epigastric pain without radiation that compelled him to halt. Later in the day the pain recurred as he took another walk. That night he was awakened several hours after retiring by the same nonradiating epigastric pain, lasting ten minutes. During the following week he was awakened every night by similar pain. A few days after he began to take alkali after meals, the nocturnal pain remitted.

He was examined four weeks after the onset of these symptoms. There was no abdominal tenderness. Fluoroscopic study revealed a heart normal in size and configuration. The heart sounds were of good quality; there were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The electrocardiogram showed a diphasic T wave in lead IV. After resting in bed for two weeks he noted that walking one or two blocks would bring on pain under the xiphoid process, radiating upward toward the neck and, on occasions, compelling him to rest. He complained no further of nocturnal pain or of postprandial epigastric pain. The anginal pain now was located either under the lower part of the sternum or under the xiphoid process, whereas a few weeks previously it was epigastric in location. An electrocardiogram taken four weeks after the first one showed further inversion of the T wave in lead IV.

This case history illustrates the original abdominal location of anginal pain in a patient with an old peptic ulcer. Subsequently the anginal pain was confined to the usual coronary pathway.

Case 12.—A man, M. U., beginning in his thirty-second year had had epigastric pain four hours after meals, unrelieved by food and often accompanied with vomiting. At the age of 46 he underwent an operation for gastric ulcer. Following the operation he remained well for six years and then began to have rare recurrences of nausea with vomiting, with remissions, up to the age of 60. Five weeks before he was first seen by us (at the age of 60) he complained of constant pain and stiffness of the left shoulder. Two weeks later, while taking a walk he suddenly experienced pain diffusely throughout the right side of the chest, radiating across the midthoracic region to the epigastrium, which compelled him to halt. He thereupon vomited much saliva and bile-stained gastric contents. This afforded him great relief. He felt well the next day, but two weeks later he suffered a recurrent attack of pain and vomiting, lasting fifteen minutes. In the interval between these attacks there were no symptoms of ulcer, but walking 3 to 4 blocks, especially hurriedly, would provoke pain in the right upper region of the chest, always associated with epigastric pressure and compelling him to rest.

He was a thin, sallow man. The lungs were emphysematous; there was no abdominal tenderness. Fluoroscopic study revealed a heart normal in size and configuration. The heart sounds were of good quality; there were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The electrocardiogram showed slurring of the QRS in all leads, a depressed RT segment and a diphasic T wave in lead IV. During the next months he again experienced pain four hours after meals, immediately relieved by food. The pain was always felt first in the right side of the chest or in the lower substernal area; it then radiated to the epigastrium

and was at times associated with mild cough or belching. The patient stated that the area just to the right of the middle of the sternum had been his "Achilles' heel" since an attack of influenza in 1918. Subsequently, whenever he suffered any infection of the upper respiratory tract he would feel pain first in this area and on coughing would feel as though the sputum were coming from this same spot. Beginning shortly after the onset of the anginal pain on effort, the slightest excitement or emotional upset would provoke the same pattern of pain, beginning at the right parasternal area, radiating to the epigastrium and associated with belching.

The foregoing case history illustrates the radiation of pain in the chest to the epigastrium, as well as the ulcer-like component of vomiting, during the first episode of angina pectoris. The anginal pain was localized to an area in the right side of the chest sensitized twenty-two years previously by an attack of influenza.

CASE 13.—A man, M. C., from his twenty-eighth to his thirtieth year was often awakened from sleep at 2 a. m. by heart burn high in the epigastrium, which was relieved by drinking hot water. At the age of 35 he was awakened one night by epigastric pain which lasted until relieved by alkali and a hypodermic injection after one hour. At the age of 50, six months before coming under our observation and while engaged at his usual work he suddenly experienced pain in the epigastrium and the lower anterior part of the chest and vomited food he had recently eaten. He took sodium bicarbonate and was relieved of pain in about half an hour. During the succeeding five months he made no complaints and suffered neither thoracic nor abdominal pain. Then, one day, while rushing to catch a train he experienced severe pain in both hypochondriac areas, radiating to both arms. A short enforced rest brought relief. Since this episode, walking 2 blocks would provoke epigastric pain radiating to both arms, forcing him to halt. He experienced no pain during his routine work.

Physical examination two weeks after the incident of pain on rushing for a train revealed no abnormality in the abdomen. Fluoroscopic examination revealed a heart of normal size and configuration; there was moderate general dilatation of the aortic arch. The heart sounds were of good quality. A faint systolic murmur was heard at the apex. The blood pressure was 100 systolic and 70 diastolic. The electrocardiogram was normal. For the next eight months symptoms were mild and consisted of infrequent pain high in the epigastrium, occurring one-half to one hour after meals as well as on walking 3 to 4 blocks. Then, while at work, at 2 p. m., one-half hour after a light lunch he experienced sudden epigastric pain radiating to the entire anterior part of the chest and to both upper extremities, lasting about ten minutes. Three days later he suffered two recurrences of similar but more severe pain, the first lasting fifteen minutes. The first attack was characterized by epigastric pain alone and lasted twelve hours. Since this episode, walking as little as 50 feet (15 meters) would provoke the epigastric pain radiating to both upper extremities, compelling him to rest, with quick relief. Glyceryl trinitrate relieved the pain. Physical examination now revealed a palpable, slightly tender liver and dulness of the heart sounds. There were alterations in the electrocardiogram, with Q waves and inverted T waves in leads II and III, and evidences of recent infarction of the posterior aspect of the left ventricle. During a four week period of rest at home he suffered no pain, but on leaving home and walking 1 or 2 blocks he experienced the same pressure pain, high up in the epigastrium, compelling him to rest. Glyceryl trinitrate again was effective in abolishing the pain.

The development of progressive myocardial damage with ultimate cardiac infarction, with pain experienced chiefly in the epigastrium, and the subsequent development of "abdominal" angina are well exemplified in the foregoing instance.

Ready Induction of Angina Pectoris During Periods of Pain from Peptic Ulcer; Less Ready Induction or Entire Remission of Anginal Pain as the Symptoms of Ulcer Are Brought Under Control by Diet and Medication.

CASE 14.—A man, H. R., at the age of 36 first experienced epigastric pain about one and a half hours after meals. Peptic ulcer was diagnosed, and he was operated on at the age of 45. Postoperatively he remained well until the age of 51, when similar epigastric pain returned. Two years later, at the age of 53, roentgen examination showed a recurrent ulcer. At the age of 54 he complained of dyspnea on walking a few blocks and of weakness and epigastric pain during work. Physical examination at this time disclosed a well built man of good color, with slight emphysema of the lungs. Fluoroscopic study revealed slight enlargement of the left ventricle. The heart sounds were of good quality; there were no murmurs. The blood pressure was 160 systolic and 80 diastolic. The electrocardiogram was normal.

When he was 58 years of age, a renal calculus was passed spontaneously. He continued to have short episodes of pain in the right upper quadrant of the abdomen, occurring three to four hours after meals and relieved by alkali. These symptoms would last a few days at a time and would be followed by long remissions. At the age of 62 he first noted mild pressure in the lower anterior part of the chest on walking upgrade; he was not compelled to rest. Shortly after this he was awakened at 2 a. m. by pressure in the lower part of the axilla, radiating to the left pectoral fold and lasting about two hours. Examination at this time disclosed little change. There was some increase in the size of the heart, but the electrocardiogram was normal and unaltered. He was given a modified Sippy diet and alkaline powders and remained well for several months; then symptoms of ulcer recurred. At the same time effort involving the use of the right upper extremity provoked the same epigastric pain, irrespective of the hour. Several months later he had recurrence of intermittent pectoral pain on the left side, occurring as a rule at 10 a. m. and at 4 p. m., intensified by food. At that time he noted that recurrences of postprandial symptoms of both the pectoral and the epigastric type were accompanied by difficulty in walking. During periods of freedom from pain he was able to walk quite freely, as much as 10 blocks, even upgrade; whereas during a period of postprandial symptoms, walking 2 or 3 blocks, particularly upgrade, provoked bilateral pressure in the lower part of the chest, radiating to the left arm and compelling him to slow his pace.

CASE 15.—A man, M. W., had been observed at frequent intervals since 1936, when he was 48 years old. He gave no past history of ulcer or ulcer-like symptoms. In April 1936 he first complained of mild pains in the right upper extremity, lasting for a few minutes at a time and bearing no relation to effort. Two weeks after the onset of this symptom, he experienced pinching pain in the anterior part of the chest and the upper dorsal area, which lasted through the night. The next morning morphine was administered by hypodermic injection and he was ordered to bed for a week. On the ninth day after the attack, physical examination revealed a well built man of good color. The lungs were clear. There was no abdominal tenderness. Fluoroscopic study revealed slight enlargement of the left ventricle. The heart sounds were of good quality. There were no murmurs. The blood pressure was 145 systolic and 85 diastolic. The electrocardiogram showed a shallow inverted T wave in lead I. During the remainder of the year 1936 he remained relatively well, suffering only mild pain and slight limitation of motion in the right and then in the left shoulder. An electrocardiogram taken in December 1936 showed an upright T wave in lead I. The years 1937, 1938 and the first half of 1939 were characterized by freedom from symptoms; he worked freely and experienced no distress at work. In July 1939, after walking a few blocks he complained of pain at the middle of the substernal area, which forced him to halt and rest. The heart sounds were now of good quality; the blood pressure, 140 systolic and 90 diastolic. The electrocardiogram showed no abnormality, the T wave in lead I being not only upright but of normal contour and voltage. An electrocardiogram taken in November 1939 was normal. He complained of pain in the chest only on walking in the morning. In May 1940 he stated that the morning angina was unchanged and that he could walk 8 blocks readily in the afternoon. If he took glyceryl trinitrate before leaving his house, he could walk 8 blocks to the station even in the morning. Physical examination in May 1940 showed no change. The electrocardiogram revealed flattening of the T wave in lead II. In lead IV the T wave was small and inverted. There was no history of an acute or severe attack of pain in the chest. During the following eleven months there was no change in the symptoms. In April 1941 he was awakened one night by severe pain in the middle of the anterior part of the chest, which lasted about an hour and necessitated a hypodermic injection of morphine. He suffered an attack on each of the two succeeding days. He remained in bed four weeks. On examination in May 1941, the heart sounds were of good quality, and the blood pressure was 135 systolic and 80 diastolic. The electrocardiogram disclosed a shallow diphasic T wave in lead I and a more deeply inverted T wave in lead IV. There was no abdominal tenderness. Following this attack, from time to time he experienced lower substernal pain unrelated to effort and recurring about every three to five hours, particularly at 3 a. m., when the pain would awaken him. Glyceryl trinitrate afforded relief from the pain for two hours; then it would recur at 5 to 6 a. m. About four to five hours later, during the daytime, the pain would return and would be equally relieved by glyceryl trinitrate. All the attacks began as a peculiar mild distress localized about the umbilicus and quickly radiated into the substernal area. There was no associated perspiration or sensation of hunger. Walking a few blocks, and also excitement, would now induce the substernal pain directly (unaccompanied by the abdominal component). He differentiated clearly the immediate thoracic pain of effort and excitement and the abdominal-thoracic pain which occurred when he was at rest and at intervals characteristic of pain from peptic ulcer. The symptoms showed no tendency to remission for six months. Then, in November 1941, he made a habit of taking 2 drachms (7.76 Gm.) of

magnesium hydroxide at 8:30 p. m., one-half hour before retiring. Within a few days he noted that the nocturnal attacks, though of the same frequency, were of lesser intensity. In general, the attacks at rest were modified and milder while he was taking erythrol tetranitrate, from August to November 1941.

Examination in November 1941 showed minor electrocardiographic alterations but no other changes. There was no abdominal tenderness. He was now given a modified Sippy diet and aluminum hydroxide gel after meals. Three weeks later he reported that he felt stronger and better generally. Attacks of thoracic pain continued to appear at 10 a. m., 3 p. m. and 3 to 4 a. m., rarely at 7 p. m., but were distinctly milder and quickly relieved by glyceryl trinitrate. No change was noted on examination. In addition to these drugs, atropine $\frac{1}{150}$ grain (0.43 mg.) and phenobarbital ½ grain (0.032 Gm.), each three times daily, were prescribed. He was last seen in January 1942. Improvement was continuous. About once a week he was awakened at 2 to 4 a. m. by the same pressure in the lower substernal area, quickly relieved by glyceryl trinitrate. Rarely he experienced the pain at 3 to 4 p. m., when glyceryl trinitrate also brought quick relief. He had taken a capsule containing $\frac{1}{150}$ grain of atropine and ½ grain of phenobarbital regularly. He took an alkali rarely, having found that the greatest relief was obtained from the capsule alone. Physical examination showed no significant change.

CASE 16.—A man, H. B., began at the age of 46 to complain of intermittent pain in the left arm, unrelated to exertion. Two years later, while he was walking, there was a sudden onset of squeezing apical pain radiating into the left arm and compelling him to rest. This pain persisted on walking.

He was a thin man. There were healed scars at the apexes of both lungs. Fluoroscopic study revealed a heart of normal size and configuration. The sounds were of good quality, and there were no murmurs. The blood pressure was 110 systolic and 70 diastolic. The electrocardiogram showed a flat T wave in lead I, a shallow T wave in leads II and III and an inverted T wave in lead IV.

At the age of 52 he complained of midabdominal pain occurring, as a rule, two to three hours after meals and relieved by food. The pain was not felt during the night. Roentgen examination shortly after this symptom appeared revealed no ulcer. Frequently with the midabdominal pain he experienced severe pain in the lower substernal and subxiphoid regions. The pain would be so severe and compelling as to force him to eat something for relief. He was given a modified Sippy diet, a colloidal suspension of aluminum hydroxide and atropine. Two months later he reported that after he began taking these medicines the hunger pains which occurred two hours after meals remitted and that he walked more freely as much as 5 blocks. Formerly he had been able to walk at best 1 or 2 blocks; then he would be stopped by abdominal distention radiating into the lower part of the chest as pain. An electrocardiogram taken at this time showed some change. The T wave in lead I was upright but of low voltage; it was diphasic in lead IV.

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PROTECTIVE ACTION OF VITAMIN C AGAINST EXPERIMENTAL HEPATIC DAMAGE

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An associate and I [1] previously found that if a hepatoxin, carbon tetrachloride, were given to dogs they could be made to excrete all instead of about half of a given dose of the sympathomimetic amine amphetamine. More recently I showed that if dogs were put on a maintenance dose of the amine, saturating the animals with vitamin C (ascorbic acid) would reduce the excretion of amphetamine to about one third of the amount normally excreted.[2] This together with the in vitro deamination of the amine demonstrated the role of ascorbic acid in the detoxication of these compounds. However, to our surprise, if dogs saturated with vitamin C were given carbon tetrachloride orally, the excretion of amphetamine did not rise above normal.

These observations suggested that ascorbic acid might protect the animals against the toxic action of carbon tetrachloride on the liver. It was deemed more suitable to turn to guinea pigs for the pursuit of the problem. The purpose of this study, then, has been to determine whether ascorbic acid administered to a group of guinea pigs maintained on a scorbutogenic diet would protect them against hepatic damage.

PROCEDURE

All the animals were maintained on a diet of Purina mixed rabbit chow checkers,[3] which is quite adequate except for vitamin C. In some instances the pellets of food were ground and mixed with 5 per cent brewers' yeast to supplement the vitamin B complex without influencing the results. Ecker and Pillemer [4] have reported that guinea pigs maintained on a similar diet showed signs of scurvy in twenty-one days and that 10 to 20 mg. of ascorbic acid per day was necessary to maintain maximal plasma concentration of the vitamin. Throughout the experiments the animals receiving ascorbic acid were given 30 mg. daily. This was made up with half its weight of sodium bicarbonate, dissolved in an equivalent of 1 cc. of distilled water and injected subcutaneously immediately.

Hydrazine sulfate was selected for the experimental production of hepatic damage, for Wells [5] has shown that it is a poison with an almost specific effect on the cytoplasm of the parenchymatous cells of the liver. When this chemical is given, the liver alone evidences structural alterations. The substance attacks the cytoplasm primarily, only much later affecting the nucleus, and causes profound fatty degeneration. The urinary products of dogs seem quite normal after a 50 mg. per kilogram dose of hydrazine sulfate, according to Underhill and Kleiner.[6]

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1. Beyer, K. H., and Skinner, J. T.: The Detoxication and Excretion of Beta Phenylisopropylamine (Benzedrine), J. Pharmacol. & Exper. Therap. **68**:419 (April) 1940.

2. Beyer, K. H.: The Action of Vitamin C and Phenol Oxidase in the Inactivation of Beta Phenylisopropylamine, J. Pharmacol. & Exper. Therap. **71**:394 (April) 1941.

3. The composition of the diet was as follows: protein, 15.35 per cent; fat, 2.38 per cent; carbohydrates, 64.61 per cent (including 16.86 per cent fiber); calcium carbonate; phosphorus; sodium chloride; potassium iodide; magnesium sulfate, and per pound (0.5 Kg.) approximately 5,000 international units of vitamin A, approximately 400 international units of vitamin B_1, approximately 3,000 micrograms of riboflavin (vitamin B_2) and negligible vitamin C.

4. Ecker, E. E., and Pillemer, L.: Vitamin C Requirement of the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **44**:262 (May) 1940.

5. Wells, H. G.: The Pathological Anatomy of Hydrazine Poisoning, J. Exper. Med. **10**:457 (July) 1908.

6. Underhill, F. P., and Kleiner, J. S.: The Influence of Hydrazine upon Intermediary Metabolism in the Dog, J. Biol. Chem. **4**:165 (Feb.) 1908.

The experiment was set up as follows: For purposes of comparison it was necessary to know the percentage of lipoid in the livers of normal guinea pigs, of ones rendered deficient in vitamin C and of ones given an injection of 30 mg. of ascorbic acid per day. This was to determine whether low or high intake of the vitamin influenced the lipoid content of the liver. To determine whether vitamin C protected the animals against hepatic damage caused by hydrazine other guinea pigs weighing between 250 and 400 Gm. were divided into two groups of 6 or more each. Both groups were placed on the vitamin C–deficient diet, and their gain in weight was followed every other day. One group (A) received 30 mg. of ascorbic acid subcutaneously daily. The other group (B) did not receive injections of the vitamin. At first the gain in weight in both groups was the same, but later the animals in group A gained more rapidly than did the ones in group B. After about sixteen days the guinea pigs in group B ceased to gain weight. Then the guinea pigs in both groups were given injections of 25 mg. of hydrazine sulfate per kilogram of body weight on two successive days. Two days after the second injection of hydrazine the animals were killed and autopsied. The livers were removed from the bodies, examined grossly and in many instances photographed with kodachrome film for future reference. After that, the livers were weighed and a section was preserved for histologic study. A weighed amount of the remainder of each liver was dried in an oven, weighed again and powdered for extraction of the lipoid fraction. The lipoids of a weighed amount of liver from each guinea pig were extracted

TABLE 1.—*Analysis of Livers from Normal Guinea Pigs*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
N-1	4.2	32.8	9.1
N-2	4.1	36.2	9.7
N-3	3.8	31.2	9.9
N-4	3.8	30.5	8.0
N-5	3.5	30.7	9.3
N-6	3.9	32.3	11.0
N-7	3.7	30.0	13.5
N-8	3.6	26.0	14.0
N-9	3.2	28.3	12.3
N-10	4.3	32.3	11.9
N-11	2.7	45.0	8.8
N-12	4.0	38.8	7.5
N-13	4.7	30.2	9.2
N-14	4.9	29.6	9.1
Average	3.9	32.5	10.2

with chloroform in a modified Soxhlet continuous extractor, the period of extraction being twenty-four hours, and at least two determinations were made on each sample of liver. After extraction the chloroform was allowed to evaporate from the lipoid fraction at 80 to 90 F.; the residue was weighed and calculated as a percentage of the dry weight of liver. Thus anatomic and chemical evidence of any damage done to the livers was obtained.

RESULTS

Analysis of Normal Livers.—The results of analysis of the livers of 10 normal guinea pigs are given in table 1. The washed livers removed from the bodies of normal guinea pigs represented an average of 3.9 per cent of the body weight, the dry matter 32.5 per cent of the total liver weight and the lipoids 10.2 per cent of the dry matter. Control values for livers from 10 guinea pigs receiving 30 mg. of ascorbic acid subcutaneously for sixteen days are given in table 2. Comparing tables 1 and 2, one can see that the data in the latter table agree remarkably closely with those for the normal guinea pigs.

In an effort to help clear up an uncertainty [7] about the effect of avitaminosis C on hepatic fat and for comparison with other data, 18 guinea pigs were maintained

7. Spellberg, M. A., and Keeton, R. W.: Production of Fatty Livers in Guinea Pigs with Scorbutogenic Diets, Proc. Soc. Exper. Biol. & Med. **41**:570 (June) 1939.

on the vitamin C–deficient diet for sixteen days and then killed, and their livers were examined and analyzed. Grossly, these livers were no different from those of normal guinea pigs. If one expresses the relation as percentage of body weight, the livers from deficient and from normal guinea pigs were similar. On the basis of these data the livers of vitamin C–deficient animals tended to have a higher lipoid content than did those of animals on an adequate diet, but the difference was not significant, especially since only 7 of the 18 vitamin C–deficient animals had a

TABLE 2.—*Analysis of Livers from Guinea Pigs Given Injections of Ascorbic Acid*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
H-1	3.9	28.4	9.8
H-2	5.0	24.3	9.9
H-3	4.9	28.8	11.1
H-4	3.7	28.8	11.1
H-5	5.3	28.3	10.8
H-6	3.9	30.4	10.0
H-7	3.4	30.8	14.0
H-8	3.7	29.5	12.8
H-9	3.7	31.3	11.8
H-10	3.8	25.6	14.0
Average	4.0	28.6	11.5

TABLE 3.—*Analysis of Livers from Vitamin C–Deficient Guinea Pigs*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
D-1	3.2	24.7	10.7
D-2	3.7	28.4	13.0
D-3	3.5	29.1	12.6
D-4	3.6	32.0	14.4
D-5	4.0	29.0	17.4
D-6	5.4	27.8	12.5
D-7	5.1	21.8	11.7
D-8	2.6	23.1	9.9
D-9	4.0	21.5	9.1
D-10	2.8	21.8	9.7
D-11	4.0	25.0	12.4
D-12	4.0	27.6	15.5
D-13	4.6	22.0	13.9
D-14	3.8	23.7	14.5
D-15	4.2	26.1	12.9
D-16	4.0	23.1	11.2
D-17	3.8	22.8	12.1
D-18	4.3	25.2	12.4
Average	4.0	25.3	12.5

lipoid content above the average of 12.5 per cent for that group (table 3). On the other hand, since vitamin C deficiency does markedly impair hepatic function, one cannot entirely dismiss this slight increase.

Vitamin C and Hepatic Damage.—Having found that there is really little difference histologically or in fat content between the livers of guinea pigs that have been maintained on an adequate diet and those maintained on a vitamin C–deficient diet with or without injections of ascorbic acid, I could then examine my original hypothesis—that vitamin C protects against hepatic damage. The experiments were set up as described in the preceding section. Briefly, two groups of guinea pigs were maintained on a diet deficient in vitamin C, and one group (A)

was given daily injections of ascorbic acid. Guinea pigs in both groups received hydrazine on the same days after those in group B ceased to gain weight.

Table 4 presents data on 19 vitamin C–deficient guinea pigs, each of which was given a total of 50 mg. of hydrazine sulfate per kilogram of body weight

TABLE 4.—*Analysis of Livers from Vitamin C–Deficient Guinea Pigs Given Injections of Hydrazine*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
DH-1	10.2	14.8	20.0
DH-2	5.0	29.4	16.2
DH-3	5.5	19.3	22.6
DH-4	5.3	26.4	27.5
DH-5	6.4	23.5	19.0
DH-6	5.7	24.0	19.8
DH-7	4.3	26.8	18.9
DH-8	4.4	26.0	20.0
DH-9	4.0	24.5	17.4
DH-10	5.9	26.6	25.8
DH-11	5.2	22.3	29.8
DH-12	7.1	21.8	30.0
DH-13	5.5	25.7	23.2
DH-14	5.1	21.4	20.5
DH-15	4.7	26.6	24.3
DH-16	5.3	23.7	17.0
DH-17	5.3	22.0	24.0
DH-18	4.5	29.6	34.2
DH-19	4.9	29.0	31.8
Average	5.5	24.4	23.3

TABLE 5.—*Analysis of Livers from Guinea Pigs Given Both Vitamin C and Hydrazine*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
HH-1	5.5	25.0	15.5
HH-2	4.8	24.5	16.7
HH-3	4.8	27.6	13.5
HH-4	4.7	27.2	14.8
HH-5	5.6	22.0	15.8
HH-6	4.0	21.3	14.2
HH-7	4.2	21.5	15.9
HH-8	4.2	21.9	15.2
HH-9	5.0	19.0	12.0
HH-10	4.0	23.3	16.3
HH-11	3.3	22.3	15.2
HH-12	4.5	20.8	12.1
HH-13	3.8	28.2	17.8
HH-14	4.4	23.0	16.2
HH-15	4.7	19.5	14.7
HH-16	5.5	23.0	14.8
HH-17	4.2	22.5	15.4
HH-18	4.1	29.6	14.3
Average	4.5	23.4	15.5

subcutaneously. Compared to the vitamin C–deficient animals in table 3, there was a 37.5 per cent increase in the liver weight as compared to body weight in the case of the animals rendered toxic. The figures for percentage of water and dry matter are almost identical in the two sets of data. One has only to compare the lipoid content of the two groups of animals to visualize the fatty nature of the livers of the animals receiving hydrazine. There was an 86.5 per cent increase

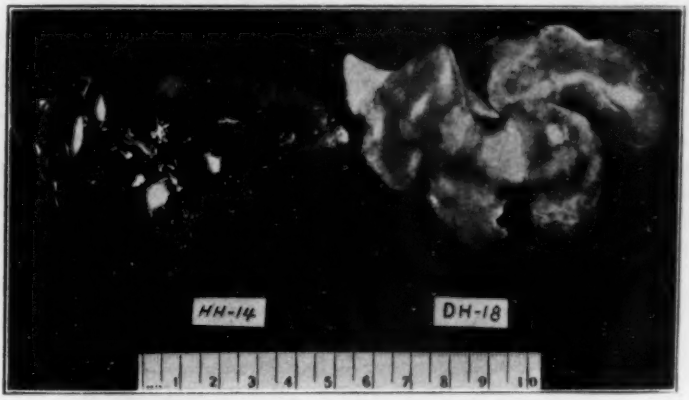

Fig. 1.—The effect of hydrazine on the livers of guinea pigs. Guinea pig HH-14 had received subcutaneous injections of 30 mg. of ascorbic acid per day. Guinea pig DH-18 had not received vitamin C. Both animals were on a scorbutogenic diet for sixteen days before being given hydrazine sulfate, 25 mg. per kilogram on two successive days. Expressed as percentage of total body weight, the liver of guinea pig DH-18 was 68 per cent heavier than that of guinea pig HH-14.

Fig. 2.—A section from the liver of guinea pig HH-14; × 100, stained with hematoxylin and eosin. This section was selected to show one lobule with the central degeneration typical of hydrazine poisoning. The architecture around the smaller central vein is more typical of the animals that have received adequate vitamin C.

in the lipoid content of the livers of vitamin C–deficient animals that received hydrazine over that of the control avitaminotic animals.

Hydrazine did increase the lipoid content of the liver in animals that received an adequate amount of vitamin C (table 5), as compared with the controls given injections of the vitamin (table 2). There was no significant increase in the weight of these livers, though the percentage of dry matter was decreased 18.2, which suggests the hydropic changes verified by histologic examination.

Finally, a comparison of tables 4 and 5 is of interest. As a result of the hydrazine poisoning those animals that did not receive an adequate amount of vitamin C showed a 22.2 per cent greater liver weight and a 50.3 per cent greater lipoid content of their livers than did the guinea pigs that received ascorbic acid.

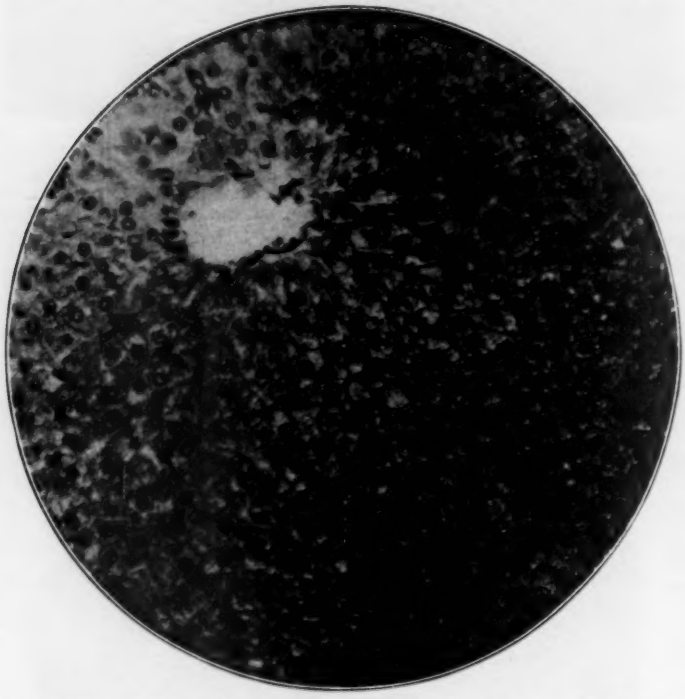

Fig. 3.—A portion of the section shown in figure 2; × 400. The cellular appearance is essentially normal. There are some hydropic changes in the cytoplasm.

Gross and Microscopic Evidence.—These analytic findings are borne out both by gross and by microscopic evidence.

Grossly, the livers of animals that received vitamin C and hydrazine were almost indistinguishable from the livers of normal guinea pigs. The livers of the guinea pigs deficient in vitamin C and given injections of hydrazine were relatively large, pale to definitely yellow, friable, somewhat hemorrhagic and yellowish on cut surfaces. Figure 1 compares the livers from 2 guinea pigs. Both animals were given injections of hydrazine, but guinea pig HH-14 received vitamin C and guinea pig DH-18 did not. The difference in size is not so apparent unless one appreciates the difference in weight of the 2 animals. Guinea pig HH-14 weighed 430 Gm., and its liver weighed 19.1 Gm. Guinea pig DH-18 weighed 290 Gm., and

its liver weighed 20.6 Gm. The paleness of the liver of guinea pig DH-18 as compared with that of guinea pig HH-14 is evident. Actually, the former liver was quite yellow.

Microscopically, it is in the livers of guinea pigs having received ascorbic acid that the early stages in the pathogenesis of this fatty degeneration due to hydrazine can be traced best. Here one sees that the process begins at the center of the lobule, decreasing in severity as it spreads toward the periphery. The process begins as a cloudy swelling of the cytoplasm. As the degeneration develops, one sees areas of condensation and rarefaction in the cytoplasm, as manifested by staining reactions; cell demarcation becomes indistinct, and the architecture of

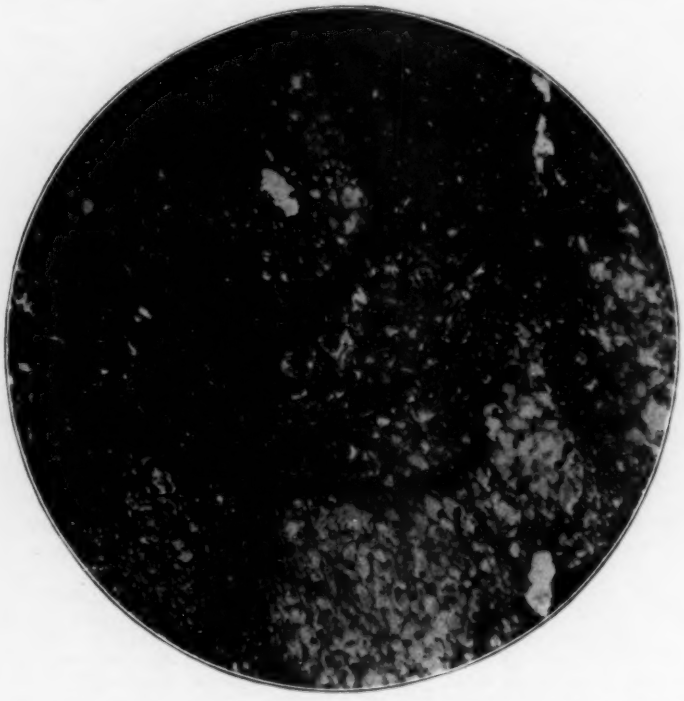

Fig. 4.—A section from the liver of vitamin C–deficient guinea pig DH-19 which had been damaged by hydrazine; × 100, stained with hematoxylin and eosin. Though the magnification is the same as that of figure 2, the increase in the size of cells, the general loss of architecture and the destruction of cells and nuclei involved in the fatty necrosis are obvious. Both this liver and that represented in figures 2 and 3 had lipoid contents approximating the average for the respective experimental groups.

the lobule becomes increasingly distorted. Finally, one may see isolated cells containing vacuoles in the cytoplasm, presumptive evidence of the presence of fat at one time. Manifestation of nuclear involvement is not apparent until relatively late in the process, and then it is one of early karyolysis. This is seldom seen in the livers of animals receiving adequate amounts of vitamin C.

Figures 2 and 3 show a section from the liver of guinea pig HH-14 at two different magnifications. The section under low power (fig. 2) has been deliberately selected to show the central involvement of the lobule typical of the patho-

genesis of this process but infrequently advanced to this degree in the livers of guinea pigs that have received vitamin C. The granular, fairly normal appearance of the cytoplasm is evident at the higher magnification (fig. 3).

Examination of sections from livers of vitamin C–deficient guinea pigs that have received hydrazine reveals the final stages in this pathogenesis. Here one sees relatively little of the early stages, for in almost all the lobules there is widespread vacuolation of the swollen cells, some of them containing nuclei having some semblance of normality and others showing only a hematoxylin-stained shell or nuclear membrane. In some lobules the process has gone on to necrosis. In these the remnants of cells are large, containing little or no cytoplasmic material

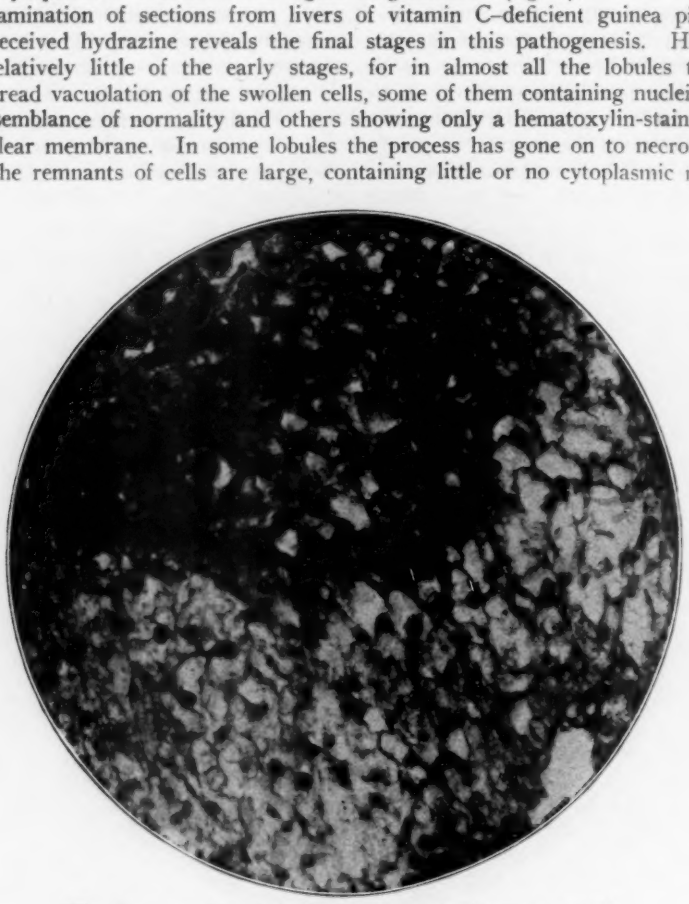

Fig. 5.—A portion of the section shown in figure 4; × 400.

and sometimes no evidence of a nucleus. These later developments are to be seen in figures 4 and 5, the magnifications of which are the same as those of figures 2 and 3, respectively.

COMMENT

It is not to be suggested that ascorbic acid supplant the use of dextrose in the treatment of acute and subacute hepatic damage. Rather, it would seem that the two substances used together would be more efficacious than either alone. There is evidence for such a viewpoint.

Beddard,[8] in 1908, was probably the first to report the use of carbohydrate in the treatment of a hepatic disease, though the work of Rosenfeld[9] also led

8. Beddard, A. P.: A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet **1**:782 (March 14) 1908.

9. Rosenfeld, G.: Fat Synthesis: Part II, Ergebn. d. Physiol. **2**:50, 1903.

him to suggest that dextrose might be beneficial in the prevention and treatment of hepatic necrosis induced by chloroform anesthesia. While the use of this form of therapy has had wide acceptance, the actual explanation of how it works is not yet clear. Recently it has been suggested that a diet emphasizing protein and carbohydrate may be better than one of carbohydrate alone.[10]

There is increasing evidence that ascorbic acid plays a significant role in the metabolism of proteins and carbohydrates in the liver, as well as in detoxication and the healing of wounds. Miwa[11] showed that in experimental scurvy the Golgi apparatus was decreased, but if ascorbic acid was given both the vitamin C level and the Golgi apparatus increased in the liver and the kidney. Also, the number of Golgi apparatus nearly paralleled the content of vitamin C in the damaged livers of rabbits. Murakami[12] found that feeding guinea pigs on a vitamin C–deficient diet decreased the excretion of bile and of bile pigment together with the detoxicating functions of the liver. If ascorbic acid was given to the animals, the disturbance in these functions was removed. In view of the present understanding of the function of the Golgi apparatus, these observations of Miwa and Murakami tend to substantiate each other.

It has been known since 1903 that leucine, tyrosine and aminoacetic acid[13] are eliminated in considerable quantities in the urine after poisoning with the hepatotoxin phosphorus, but only recently evidence has been found for a direct or an indirect participation of vitamin C in protein metabolism. Romanyuk[14] has shown that cathepsin activity of kidney, liver and muscle was increased during avitaminosis C in guinea pigs. Levine, Marples and Gordon[15] reported that some premature infants excreted parahydroxyphenyllactic acid and parahydroxyphenylpyruvic acid. If phenylalanine or tyrosine was fed to the infants, the excretion of the substances just mentioned increased, but if human milk or ascorbic acid was given in the diet, the excretion of the compounds dropped to zero. Similar results were obtained by Sealock and Silberstein,[16] who found that vitamin C–deficient guinea pigs fed 0.5 Gm. or more of tyrosine per day excreted homogentisic acid, parahydroxyphenylpyruvic acid and parahydroxyphenyllactic acid. If 10 mg. or so of ascorbic acid was fed daily to the animals, the excretion of these metabolites was prevented.

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10. (*a*) Miller, L. L., and Whipple, G. H.: Chloroform Liver Injury Increases as Protein Stores Decrease: Studies in Nitrogen Metabolism in These Dogs, Am. J. M. Sc. **199**: 204 (Feb.) 1940. (*b*) Messinger, W. J., and Hawkins, W. B.: Arsphenamine Liver Injury Modified by Diet: Protein and Carbohydrate Protective, but Fat Injurious, ibid. **199**:216 (Feb.) 1940. (*c*) Ravdin, I. S.: The Protection of the Liver from Injury, Surgery **8**:204 (Aug.) 1940.

11. Miwa, A.: Golgi's Apparatus and Vitamin C: Experimental Studies, Orient. J. Dis. Infants **26**:3 (July) 1939.

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13. Abderhalden, E., and Bergell, P.: Concerning the Elimination of Monoaminoacids in the Urine of Dogs Following Phosphorus Poisoning, Ztschr. f. physiol. Chem. **39**:464, 1903.

14. Romanyuk, N. M.: Cathepsin Activity in the Brain and Muscles During C Avitaminosis, Biochem. J. (Ukraine) **14**:354, 1940.

15. Levine, S. Z.; Marples, E., and Gordon, H. H.: Defect in the Metabolism of Aromatic Amino Acids in Premature Infants: The Role of Vitamin C, Science **90**:620 (Dec. 29) 1939.

16. Sealock, R. R., and Silberstein, H. E.: The Excretion of Homogentisic Acid and Other Tyrosine Metabolites by the Vitamin C Deficient Guinea Pig, J. Biol. Chem. **135**:251 (Aug.) 1940.

Since 1865 it has been repeatedly shown that in hepatic damage by hepatotoxins the glycogen content of the liver is rapidly and almost completely exhausted.[17] An interesting isolated observation was made by Ratsimamanga,[18] namely, that in guinea pigs maintained on a vitamin C–deficient diet liver glycogen and muscle glycogen decreased to one fifth of normal and phosphocreatine fell to one third of normal, while muscle lactate and blood lactate tended to increase. The reports of Watanabe,[19] Morelli and d'Ambrosio[20] and Terada[21] are in agreement that ascorbic acid injected into guinea pigs or rabbits increased the glycogen content of the liver. According to Watanabe, vitamin A and vitamin D had no effect and vitamin B_1 and vitamin B_2 had but slight effect on glycogen production. Hjorth[22] and Dienst[23] found that administration of vitamin C increased the dextrose tolerance of normal and of vitamin C–deficient patients. Fan and Woo[24] and Vasile and Pecorella[25] observed that in children with glycogen disease and creatinuria there was a disappearance of creatine and an increase in the excretion of creatinine in the urine if 200 mg. of ascorbic acid was fed daily. This Vasile and Pecorella attributed to an increased utilization of carbohydrate in the presence of the vitamin, resulting in an increased accumulation of glycogen in the tissues.

Since on the basis of existing evidence vitamin C does play a part in the intermediate metabolism of proteins and is necessary for the presence of Golgi apparatus and production of bile and its pigments and since its absence or presence results in a diminution or increase in the glycogen content of the liver with a decrease or increase in dextrose tolerance, it seems a definite factor in the maintenance and repair of hepatic function and structure. The experiments presented in this communication seem to bear out the theory that vitamin C does protect against hepatic damage.

SUMMARY

Analytic and histologic evidence is presented for the protective action of vitamin C against hepatic damage. Vitamin C–deficient guinea pigs showed an average of 50.3 per cent more fat in their livers than did guinea pigs receiving adequate ascorbic acid when both groups receiving the same diet were given the hepatotoxin hydrazine. Gross and microscopic evidence bore out the severity of the fatty degeneration in the vitamin C–deficient animals and the relatively mild involvement of the livers of normal guinea pigs receiving the compound.

While glycogen replacement therapy has met with the accord of time, carbohydrate utilization and glycogen storage, as well as intermediary metabolism of protein, are at least in part dependent on an adequate body content of ascorbic acid.

426 North Charter Street.

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22. Hjorth, P.: The Influence of Vitamin C on Carbohydrate Metabolism, Acta med. Scandinav. **105**:67, 1940.

23. Dienst, C.: Action of Vitamins B and C in Diabetes, Deutsche med. Wchnschr. **65**: 710 (May 5) 1939.

24. Fan, C., and Woo, T. T.: Effect of Vitamin C on Creatine and Creatinine Metabolism, Proc. Soc. Exper. Biol. & Med. **45**:90 (Oct.) 1940.

25. Vasile, B., and Pecorella, F.: The Influence of Vitamins on the Metabolism of Creatin Substances in Childhood: I. The Effect of Vitamin C, Pediatria **47**:130 (Feb.) 1939.

THE HEART IN PULMONARY EMBOLISM

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Theophilus Bonetus in his Sepulchretum in 1679 is reported by White [1] to have recorded cases of dyspnea, rapid breathing and blood spitting which presumably were due to pulmonary embolism and pulmonary infarction. However, it remained for Virchow,[2] the creator of the doctrine of embolism and thrombosis, in 1856, to record an early case in which embolism of the pulmonary arteries was described as the cause of sudden death. It is of interest to note in this report by Virchow that mention is made of the mechanism of death in pulmonary embolism. He attributed death primarily to failure of the heart as a result of a decrease of flow through the coronary arteries and stated that at necropsy the heart usually was found in the state of diastole.

More recently the mechanism of death in pulmonary embolism has been studied in experimental animals in an endeavor to determine the relative importance of mechanical and reflex factors. Dunn,[3] in 1920, reported the effect of injecting starch particles into the veins of goats. The particles lodged in the pulmonary arterioles, and death followed in five minutes to eight hours, depending on the amount of starch used. Dunn noted a rise of venous pressure, a drop of arterial pressure and an increase of respiratory rate. Section of the vagus nerve largely abolished the tachypnea, which could be reproduced again by electric stimulation of the central end of the nerve. This work was repeated by de Takáts, Beck and Fenn [4] in 1939, with similar results.

In 1923 Haggart and Walker [5] reported on quantitative closure of the pulmonary artery in cats and the effect on the functioning of the systemic circulation. It was noted that clamping of the left branch of the pulmonary artery increased the pulmonary arterial pressure 29 per cent without changing the systemic arterial pressure, the cardiac size or the cardiac output. The respiratory rate, however, increased 25 per cent. By slowly constricting the main pulmonary artery, Haggart and Walker found that about 60 per cent of the lumen could be occluded before a significant variation in the systemic circulation occurred. When more than 85 per cent of the

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4. de Takáts, G.; Beck, W. C., and Fenn, G. K.: Pulmonary Embolism: An Experimental and Clinical Study, Surgery **6**:339-367 (Sept.) 1939.

5. Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, Arch. Surg. **6**:764-783 (May) 1923.

lumen was occluded, the animals invariably died. In this regard it is of interest to note that Mann and his associates [6] demonstrated that constriction of the lumen of *small* arteries in animals may be surprisingly great without changing the rate of flow through the artery as measured by the thermostromuhr. The cross-sectional area of the lumen may be reduced 50 per cent without any change of blood flow, while a reduction of 90 per cent of the area of the lumen reduces the flow only 50 per cent.

Villaret, Justin-Besançon and Bardin [7] reported their experimental work with rabbits in 1936. They were impressed with the nervous factors involved in pulmonary embolism. They noted that by sectioning the vagus nerves of rabbits they could increase sevenfold the quantity of small particulate matter (particles of pumice stone 150 microns in diameter) necessary to produce sudden death. On the contrary, by sectioning the cervicodorsal sympathetic nerves they could produce sudden death with only a fourth as much particulate matter. The stimulus for the sudden death, which was considered to be a result of reflex action on the general circulation, was thought to arise in the terminal pulmonary arterioles. In similar experiments in which they used enamel pearls measuring from 2 to 8 mm. in diameter, they were unable to produce death, either sudden or delayed, with from 50 to 100 pearls. There was likewise no great increase of respiration in these animals such as occurred when particulate matter was used. The size of the embolizing particles thus greatly altered the results of the experiment.

In animals in which the vagus nerves had not been sectioned, Villaret and his associates were able to demonstrate a protective action by atropine sulfate and ephedrine hydrochloride used in combination, in that these drugs delayed sudden death. Chemical factors also were found to have definite effects on the length of survival of rabbits. Sodium bicarbonate increased the survival one hour to several days, while hydrochloric acid increased the susceptibility to sudden death. The authors suggested that death from pulmonary embolism is due in part to reflex sympathetic inhibition in which shock is the resultant manifestation of the inhibition.

The effect on the circulation and the heart of embolism of the main pulmonary artery or of one of its larger branches has been a much pondered question in recent years. Leriche, Fontaine and Friedmann [8] quoted statistics indicating that 30 per cent of patients dying of pulmonary embolism have small or partial occlusion of the pulmonary artery or of its branches, while de Takáts, Beck and Fenn found that 20 per cent of their patients whose death was considered typical of pulmonary embolism presented "minor" pulmonary obstruction. Death in such cases is attributed to reflex vasoconstriction of the pulmonary arterial bed through the sympathetic nerves, which greatly increases the strain on the right ventricle and decreases the flow of blood to the left ventricle. Leriche and his co-workers advocated infiltration of the stellate ganglion with procaine hydrochloride in cases of pulmonary embolism in an effort to release this vasoconstriction. One of us (Barnes [9]) suggested intravenous use of papaverine hydrochloride in order to release the spasm of the smooth muscle in the small pulmonary arteries. Jesser

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8. Leriche, R.; Fontaine, R., and Friedmann, L.: L'infiltration stellaire est-elle justifiée dans l'embolie pulmonaire du point de vue physiologique et anatomo-pathologique? Quelle place doit-elle occuper dans la thérapeutique de cette affection? J. de chir. **50**:737-748 (Dec.) 1937.

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and de Takáts [10] recently presented experimental evidence which strongly supports the value of papaverine in overcoming the constriction of the pulmonary arterial tree in pulmonary embolism. Likewise they found that powerful bronchial constriction occurs in dogs and that this often is abolished by atropine in sufficient doses and, to a less extent, by papaverine.[11]

The possibility of a pulmonocoronary reflex has been postulated by Scherf and Schönbrunner,[12] who demonstrated electrocardiographic changes in 2 of 10 dogs in which pulmonary embolism was produced. The changes in the electrocardiogram were interpreted as evidence of decreased flow through the coronary arteries. As further suggestive evidence of decreased flow through the coronary arteries following pulmonary embolism, they cited 2 cases in which angina pectoris developed after the embolism. The pain in each of these 2 cases was relieved by nitrite.

Indirect evidence of some type of nervous reflex has been presented by de Takáts, Beck and Fenn in the experimental field. Dogs subjected to massive pulmonary embolism died immediately after the embolism in 100 per cent of the experiments. Survival of 68 per cent of animals from ten minutes to twenty-four hours was obtained by immediate intravenous injection of a solution of atropine salt; similar results were obtained in 60 per cent of the animals by the use of papaverine. The action of atropine suggests the abolition of some undesirable vagal reflex, while papaverine acts directly on the smooth muscle of the pulmonary arteries, thus decreasing the strain on the right ventricle.

Experimental attempts to produce death in animals without occlusion of the major portion of the pulmonary artery by emboli have been unsatisfactory. Mann,[13] in 1917, endeavored to produce sudden death in dogs by introducing emboli (paraffin and blood clots) into both anesthetized and unanesthetized animals. He was concerned to find out whether emboli obstructing a relatively small portion of the pulmonary circuit could cause sudden death. The results of all the experiments were the same. In order to produce death or to imperil the life of the animal seriously, he found it imperative to obstruct the pulmonary artery greatly, either with one large embolus or with multiple small emboli. In each instance in which death occurred, necropsy revealed "almost complete" obstruction of the pulmonary circuit. Hall and Ettinger [14] arrived at similar conclusions in 1933 with similar experiments. These authors also attempted to demonstrate a reflex on the heart of stimuli originating in the wall of the pulmonary artery and mediated by medullary centers which might account for sudden death. The pulmonary artery was distended, both with and without occlusion, but no effect was demonstrated on aortic blood pressure, cardiac rate or output per beat.

The electrocardiographic changes found in typical cases of pulmonary embolism have been defined by McGinn and White [15] and by Barnes.[16] McGinn and White

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12. Scherf, D., and Schönbrunner, E.: (*a*) Ueber Herzbefunde bei Lungenembolien, Ztschr. f. klin. Med. **128**:455-471, 1935; (*b*) Ueber den pulmocoronaren Reflex bei Lungenembolien, Klin. Wchnschr. **16**:340-344 (March 6) 1937.

13. Mann, F. C.: Pulmonary Embolism: An Experimental Study, J. Exper. Med. **26**:387-394 (Sept.) 1917.

14. Hall, G. E., and Ettinger, G. H.: An Experimental Study of Pulmonary Embolism, Canad. M. A. J. **28**:357-368 (April) 1933.

15. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting from Pulmonary Embolism: Its Clinical Recognition, J. A. M. A. **104**:1473-1480 (April 27) 1935.

16. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**:11-13 (Jan. 2) 1936.

suggested that probably the changes in the electrocardiogram were due to "dilatation and partial failure of the chambers of the right side of the heart." These authors observed the following electrocardiographic changes in cases of pulmonary embolism: (1) prominent S_1 with S-T segment starting slightly below the base line; (2) depressed RS-T segment in lead II with gradual ascent from the S to the T wave in lead II; (3) usually a diphasic or monophasic T_2; (4) Q wave and definite inversion of T wave in lead III; (5) positive T wave, occasionally diphasic, in Wolferth lead. It must be remembered that a typical case of pulmonary embolism may present all of these features, while cases in which there are smaller emboli may present any one or more characteristics of the electrocardiographic pattern.

Although strain on the right ventricle with or without resultant failure plays some role, it has been pointed out by various authors that other factors possibly come into play in the complicated physiologic consequences of pulmonary embolism. Edens was credited by Horn, Dack and Friedberg [17] with first suggesting that vagal stimulation rather than obstruction of the pulmonary artery is responsible for cardiac dysfunction and death, although no mention is made of this effect on the electrocardiogram. Scherf and Schönbrunner [12a] attributed the electrocardiographic changes from 2 of 10 dogs in which experimental pulmonary embolism had been produced to reflex constriction of the coronary arteries with resultant decreased coronary flow. Love and Brugler [18] suggested other than mechanical factors, such as anoxemia of the heart muscle, reflex changes in coronary circulation and the preexisting state of the coronary arteries.

Love, Brugler and Winslow,[19] using dogs, studied the electrocardiographic changes occurring after experimental pulmonary embolism and emphasized the element of shock and the status of the coronary arteries in the electrocardiographic picture. Shock produced by hemorrhage was found not to alter the electrocardiogram. By partially ligating the anterior descending coronary artery and then inducing shock by hemorrhage, they produced elevation of the RS-T segment in leads II and III, simulating coronary occlusion. Experimental embolization in 13 dogs revealed that depression of the S-T segment in lead II was the finding of most significance, which at times was accompanied by inversion of the T waves in leads II and III. Comparable results were obtained by mechanical obstruction applied externally to the pulmonary artery. No alteration of these electrocardiographic findings was noted after vagal or sympathetic denervation.

Anatomic changes in the hearts of patients who died of pulmonary embolism have been described recently. Horn, Dack and Friedberg studied the records of 42 cases of pulmonary embolism and found structural myocardial changes "ordinarily resulting from acute myocardial ischemia" in 8 (minimal in 4). The location of these changes they did not define except to state that the sections were taken from the left ventricle. The electrocardiographic pattern in cases of pulmonary embolism is attributed by these authors to myocardial ischemia from coronary insufficiency as a result of the interplay of three probable factors: (1) shock, (2) asphyxia and (3) exaggerated vagal reflexes from obstruction of the pulmonary arteries. The similarity of the electrocardiographic changes in cases of pulmonary embolism and cases of myocardial infarction of the posterior wall

17. Horn, H.; Dack, S., and Friedberg, C. K.: Cardiac Sequelae of Embolism of the Pulmonary Artery, Arch. Int. Med. **64**:296-321 (Aug.) 1939.

18. Love, W. S., Jr., and Brugler, G. W.: Electrocardiograms Similar to Those of Coronary Thrombosis with Especial Reference to Those Obtained in Pulmonary Embolism, South. M. J. **30**:371-375 (April) 1937.

19. Love, W. S., Jr.; Brugler, G. W., and Winslow, N.: Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization, Ann. Int. Med. **112**:2109-2123 (June) 1938.

of the left ventricle is attributed by those authors to diminished flow through the right coronary artery resulting from increased tension in the right ventricle.

The purpose in the present investigation is to study the heart in cases of pulmonary embolism. Particular attention is given to the location of any anatomic changes and to the frequency of these changes. A correlation of interesting electrocardiographic alterations with anatomic abnormalities is made.

METHOD OF STUDY

Protocols from a six year period (1935-1941) were consulted and 307 cases of pulmonary embolism were studied. The cases were divided roughly into surgical (70 per cent), medical (20 per cent) and cardiac (10 per cent). The number of surgical cases is unusually high compared with the data of Hampton and Castleman,[20] who gave the statistics from a large general hospital as surgical 40 per cent, medical 30 per cent and cardiac 30 per cent. Thirty cases were selected for careful anatomic study of the heart, as defined in the succeeding paragraphs. An endeavor was made to select (1) cases in which there had been clinical evidence of more than one pulmonary embolism (12), (2) cases in which there had been clinical evidence of shock for more than two hours before death (10) and (3) cases in which there was moderate to severe coronary sclerosis at necropsy (8). The embolism was considered as the primary cause of death in 26 cases and as only contributory to death in 4.

In each case the heart was examined grossly for evidence of dilatation of both auricles and ventricles and measurements were made of the thickness of the walls of each ventricle. The heart muscle was examined for evidence of fresh infarction, healing infarction and healed infarction. The interventricular septum and the posterior portion of the left ventricle were sectioned as well as the anterior portion of the left ventricle. At least six sections were made for microscopic examination as follows: (1) the anterior portion of the left ventricle, (2) the anterior portion of the right ventricle, (3) the posterior portion of the right ventricle, (4) the posterior basilar portion of the left ventricle, (5) the interventricular septum and (6) the posterior papillary muscle. A few sections were made of the anterior papillary muscle, and sections were taken from any scarred region or one suspicious of fresh infarction. The coronary arteries were then examined, and each artery together with its major branches was cut crosswise at least every 5 mm. Sections were taken from the artery in any region where there was significant encroachment on the lumen of the artery or where there was evidence of a thrombus. The distribution of each artery was noted, and, especially in regard to the posterior region of the left ventricle, note was made as to whether the right coronary or the left circumflex coronary artery supplied this portion.

The sections of heart muscle were examined microscopically for evidence of acute infarction or healing infarction which might have occurred concomitantly with a clinical episode of pulmonary embolism. In the study of any healing process of the myocardium, advantage was taken of the Van Gieson stain for fibrous tissue in estimating the age of the infarct.

RESULTS

In the study of 307 cases in which emboli were found in the pulmonary arteries at necropsy, the heart was found to weigh more than 400 Gm. in about a third of the cases. This did not include those in which there had been valvular or pericardial disease and was considered as evidence to indicate that there had been hypertension. When the medical cases were discarded and only the surgical ones were considered, the percentage in which the heart weighed more than 400 Gm. remained about the same (fig. 1).

Since practically all the patients who had had pulmonary embolism had been 50 or more years of age, a control group was studied of patients more than 50 years of age who had undergone a surgical operation and who had died of some cause other than pulmonary embolism (fig. 2). No significant difference in percentage of cases in which the heart weighed more than 400 Gm. was noted in the surgical group with pulmonary embolism and a control group with the same age distribution,

20. Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings, with Special Reference to Pulmonary Embolism and Infarction, Am. J. Roentgenol. **43**:305-326 (March) 1940.

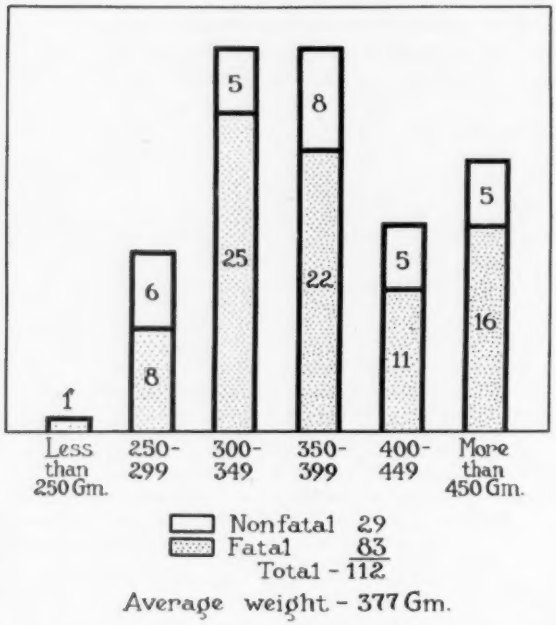

Fig. 1.—Weights of the hearts of surgical patients who had pulmonary embolism.

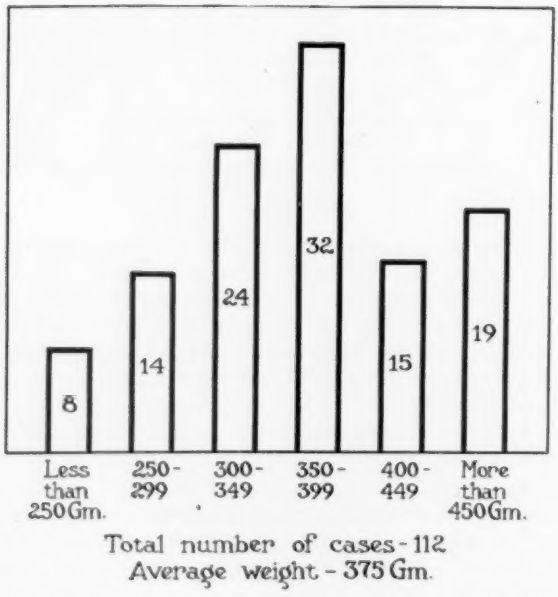

Fig. 2.—Weights of the hearts of surgical patients more than 50 years of age and without pulmonary embolism.

and the average weight of the heart in the two groups was almost the same. Thus it may be concluded that among patients who had enlarged hearts and who underwent a surgical operation pulmonary embolism was no more likely to develop than among patients who had hearts of normal weight. If it is admitted that in this study hypertrophied hearts were considered to indicate hypertensive vascular disease, it is apparent that hypertension did not predispose to pulmonary embolism (figs. 1 and 2).

The medical cases in which pulmonary embolism occurred consisted mainly of two groups: those in which there was heart disease with signs of congestive heart failure most commonly due to hypertensive heart disease alone or combined with coronary sclerosis, and those in which there was some wasting disease (cancer or senility). The curve of the weight of the heart for the medical group (fig. 3) is

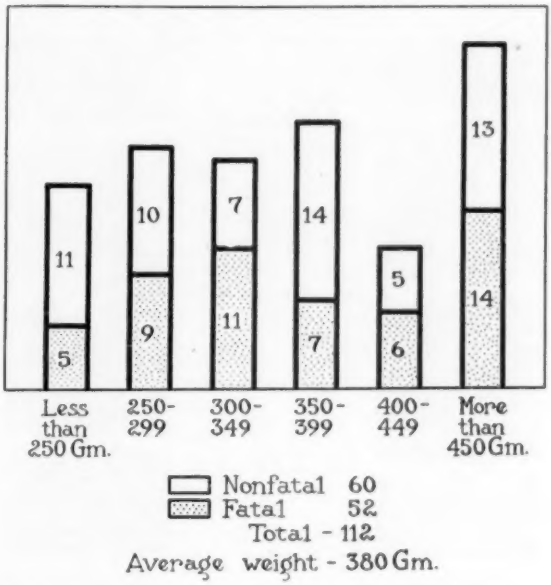

Fig. 3.—Weights of the hearts of medical patients who had pulmonary embolism.

considerably "flatter" than that for the surgical group, since in the group of cases in which there was a wasting disease the number in which the heart weighed less than 250 Gm. tended to increase and in the group of cases in which there was hypertension the opposite was observed. It also will be noted that the percentage of cases in which the pulmonary embolism was fatal was considerably less in the medical group (46 per cent) than it was in the surgical group (74 per cent). This confirms the general clinical impression that the percentage of cases with fatal pulmonary embolism is greater in the surgical than in the medical group.

Among the 30 cases of pulmonary embolism studied, there were 5 in which the anatomic changes in the heart muscles were significant. They are presented here.

Myocardial Infarction Without Coronary Occlusion.—In 4 cases recent myocardial infarction was observed, but no thrombosis or occlusion of the coronary arteries could be demonstrated. The location and extent of the infarction varied.

Case 1.—A 64 year old man was admitted to the hospital for litholapaxy and transurethral prostatic resection. His history did not suggest previous heart disease, and his blood pressure was 130 mm. of mercury systolic and 80 diastolic. Operation was performed, with the patient under spinal anesthesia, on Nov. 18, 1940. November 20, on returning to bed after sitting in a chair, he became weak, his pulse rate rose to 130, his respiratory rate increased to 36, and he appeared cyanotic. The temperature rose to 103 F. His condition was improved considerably after he had spent eight hours in an oxygen tent, at which time the blood pressure was 125 mm. of mercury systolic and 80 diastolic. An electrocardiogram taken on November 21 revealed a typical Q_3 T_3 pattern with a slight lengthening of the S wave in lead I (fig. 4). On November 24 the patient raised small amounts of bright red sputum. Convalescence was uneventful thereafter until December 5, when he complained of a pleuritic pain in the lower right portion of the chest. On the following day he experienced tenderness in the right calf, and the temperature rose to 101 F., although the right leg did not become swollen. The temperature returned to normal on the following day, and

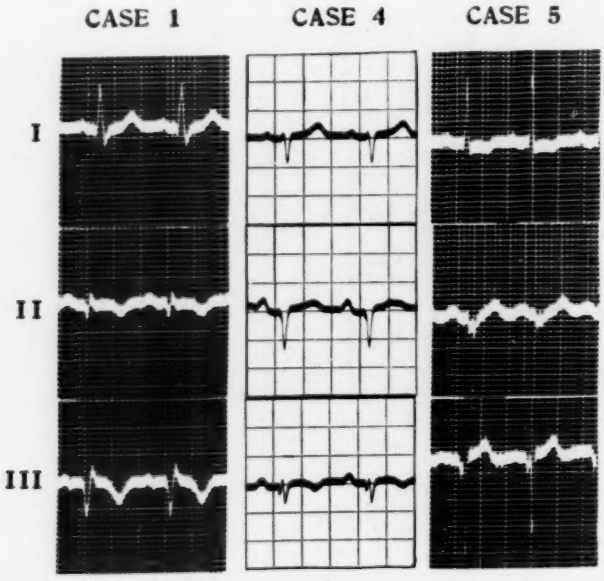

Fig. 4.—Case 1. The electrocardiogram was taken one day after an episode of pulmonary embolism and presents a typical Q wave–T wave pattern in lead III plus slight prolongation of the S wave in lead I.

Case 4.—The electrocardiogram, taken on the day of death, presents a much elongated S wave in lead I and a small Q wave and an inverted T wave in lead III. The greater deflection in each lead is negative.

Case 5.—This tracing, taken before the onset of pulmonary edema and ten hours before death, reveals only evidence of left ventricular strain and nothing to suggest pulmonary embolism or myocardial infarction.

the patient was improving until he suddenly collapsed, became cyanotic and dyspneic, and died within thirty-five minutes, on December 8.

The anatomic diagnosis was (1) fatal pulmonary embolism (source, right iliac vein) (residual thrombus in left iliac vein), (2) multiple pulmonary infarcts with focal pleuritis, (3) hypertrophy of the heart (580 Gm.), (4) healed myocardial infarction of the anterior portion of the interventricular septum (6 by 3 cm.) and healing recent myocardial infarction of the posterior portion of the left ventricle adjacent to the interventricular septum (focal) and the posterior portion of the right ventricle (2 by 2.5 cm.).

The right coronary artery supplied the posterior basilar portion of the left ventricle and was patent throughout. The sclerosis was graded 1 (on the basis of 1 to 4, in which 1

designates the least amount of sclerosis and 4 the greatest). The left circumflex artery was patent, and the sclerosis was graded 2. Five centimeters from the orifice of the left descending coronary artery was an old thrombus, which had become recanalized but which occluded about 95 per cent of the lumen of the artery. Sclerosis of this artery was graded 3. The region of recent infarction in the posterior portion of the right ventricle was located in the apical third and was recognized grossly (fig. 5 *a*). Microscopic examination of this region revealed loose connective tissue, which did not take the Van Gieson stain, and occasional collections of lymphocytes. There were a few small scattered regions in the posterior portion of the left ventricle which appeared fibrotic and which on microscopic examination proved to be regions of recent infarction. They were present in both the apical and the basilar portions (fig. 5 *b*). No polymorphonuclear leukocytes were found. The age of these infarctions was estimated at about three weeks.[21]

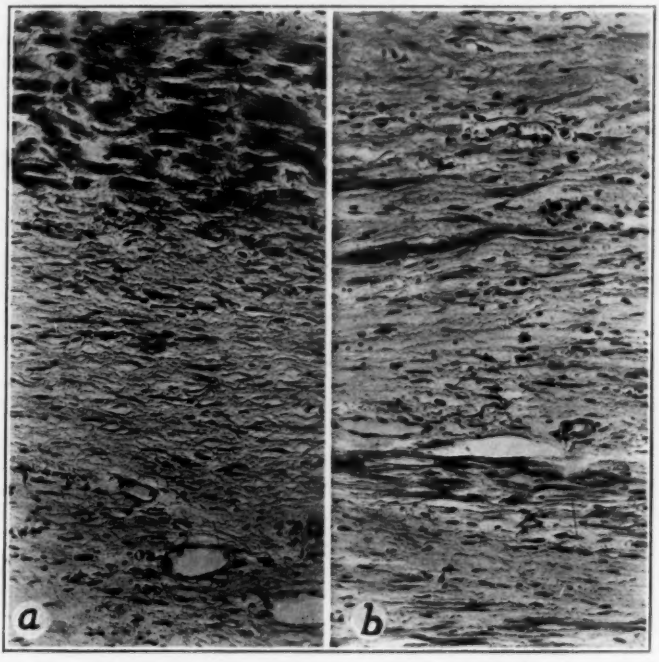

Fig. 5.—(*a*) Section from the posterior portion of the right ventricle close to the epicardial surface, representing healing infarction. The loose fibrous tissue does not take the Van Gieson stain. (*b*) Section from the posterior portion of the left ventricle close to the interventricular septum demonstrated focal healing infarction. The fibrous tissue does not stain with the Van Gieson stain and is of approximately the same age as that in *a*.

Case 1 illustrates the difficulties which may present themselves at times to one making a diagnosis of pulmonary embolism. The clinical picture of tachycardia, dyspnea and cyanosis, followed on the fifth day by the spitting of blood, was sufficient to allow a diagnosis of pulmonary embolism with pulmonary infarction to be made. Yet the electrocardiogram taken on the second day presented the typical Q_3 T_3 pattern of myocardial infarction of the posterior wall. It will be

21. Mallory, G. K.; White, P. D., and Salcedo-Salgar, J.: The Speed of Healing of Myocardial Infarction: A Study of the Pathologic Anatomy in Seventy-Two Cases, Am. Heart J. **18**:647-671 (Dec.) 1939.

noted, however, that the S wave in lead I measures 2 mm., which might be construed as evidence of pulmonary embolism. Since no thrombosis or occlusion was found in the right coronary artery supplying the posterior portion of the heart, it seems justifiable to assume that the regions of recent infarction which were found resulted from a decrease in blood flow to these portions of the heart at the time of the pulmonary embolism.

CASE 2.—A 53 year old woman entered the hospital, complaining of epigastric pain and gas immediately after eating, of six weeks' duration. During the preceding year she had lost 40 pounds (18 Kg.). Her history did not suggest heart disease, and her blood pressure was 140 mm. of mercury systolic and 90 diastolic. The heart was normal to examination. There was a large irregular nodular mass which seemed to fill the epigastrium and was not attached to the liver. On May 7, 1940, redness and pain developed over the dorsum of the right foot, and in this region a firm, tender vein was palpated. Abdominal exploration was performed on May 10, and on the following day the patient complained of pain in the whole left leg, which soon was swollen and cyanotic. Tenderness along the femoral vein was noted on May 12. On May 13 the patient became nauseated and vomited, but the pulse rate continued about the same, ranging between 100 and 120. The patient became cold, sweaty and semistuporous and died on May 15. The blood pressure was recorded as 70 mm. of mercury systolic and 50 diastolic six hours before death.

The anatomic diagnosis was (1) carcinoma of the stomach (linitis plastica type) with abdominal and peritoneal carcinomatosis and metastasis to the periaortic lymph nodes and the right adrenal gland, (2) pulmonary embolism of the right lung with pulmonary infarcts (source, thrombosis of both iliac veins with extension into the inferior vena cava), (3) hypertrophy of the heart (390 Gm.) and (4) acute myocardial infarction (1.5 by 2 cm.) of the posterior base of the left ventricle, located 3 cm. from the interventricular septum.

The right coronary artery supplied the greater portion of the posterior wall of the left ventricular, including the region of acute infarction. No thrombi or occlusions were found in the coronary arteries, and the coronary sclerosis was graded as follows: left descending artery, grade 2; left circumflex artery, grade 3; right artery, grade 3. The region of acute infarction presented infiltration with polymorphonuclear cells, loss of striation of some of the muscle bundles, eosinophilic staining of some muscle and scattered regions of hemorrhage (fig. 6*a*). There were multiple small emboli in the arteries of the right lung, with one infarct, measuring 3 by 2 cm., in the upper lobe of this lung. In the main artery to the lobe of the lung there was a riding embolus occluding the artery, which showed early organization with the pulmonary artery. At least half of this lower lobe showed evidence of hemorrhagic infarction. The estimated age of both the myocardial infarction and the embolism in this lobe with pulmonary infarction was from two to four days.

In case 2 the pulmonary emboli were considered to be only contributory to death since only a part of the pulmonary arterial tree was obstructed and since death was at least partially due to the generalized carcinomatosis. Here again there was no demonstrable occlusion of the right coronary artery, which supplied the portion of the heart which was infarcted, although the sclerosis of this artery was graded 3. The most reasonable explanation for the infarction of the heart was that the flow of blood through the right coronary artery was insufficient. This was thought to be due essentially to two factors: (1) the shock which was manifest clinically for at least two days before death, and (2) the coronary sclerosis which was particularly evident in the long right coronary artery which supplied the infarcted region. Pulmonary embolism and general debility were the causative factors for the state of shock.

CASE 3.—A 57 year old woman complaining of a lump in the right breast was examined at the clinic in March 1938. Radical mastectomy was performed at this time, revealing adenocarcinoma of grade 4 (Broders' method) without involvement of the lymph nodes. She remained well until February 1939, when she noticed gradual enlargement of the abdomen and returned to the clinic in April of the same year. Her blood pressure was 140 mm. of mercury systolic and 88 diastolic, and her history was not suggestive of heart disease. At this time an irregular mass, about 5 cm. in diameter, was noted to the left of the uterus. Abdominal exploration was carried out on April 8, 1939, and extensive adeno-

carcinoma of both ovaries with peritoneal implants was revealed, and bilateral salpingo-oophorectomy was performed. On April 10, the temperature rose to 102 F., the pulse rate to 160 and the respiratory rate to 50. The patient was markedly dyspneic, and there was cyanosis of the skin. The patient was considered to have pneumonia in the lower lobe of the right lung and received sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). She continued to improve until April 22, when she suddenly became cyanotic and pulseless and died within five minutes.

The anatomic diagnosis was (1) bilateral fatal pulmonary embolism with pulmonary infarcts of the right lung (source, right femoral vein), (2) adenocarcinoma of both ovaries with peritoneal carcinomatosis (ascites, 5 liters), (3) recent myocardial infarction of the apex of the interventricular septum (0.3 cm. in diameter) and microscopic foci in the anterior wall of the right ventricle and the posterior papillary muscle, (4) bilateral hydrothorax (right, 350 cc., and left, 300 cc.) and (5) evidence of old right radical mastectomy for adenocarcinoma grade 4.

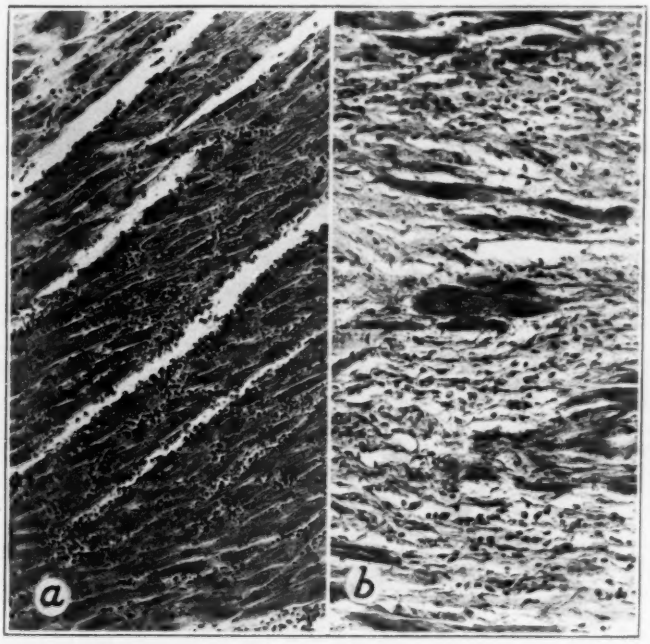

Fig. 6.—(*a*) Region of acute infarction from the posterior basilar portion of the left ventricle corresponding to that described grossly. (*b*) Section from the small region located in the interventricular septum at the apex noted grossly. The section demonstrates a recent small healing infarction.

The heart weighed 340 Gm., and the sclerosis in all the coronary arteries was graded 1. The regions of healing infarction were consistent with a healing of about two weeks (fig. 6*b*).

In case 3 the diagnosis of pulmonary embolism was not made clinically, and the patient was treated for suspected pneumonia of the lower lobe of the right lung after the rather sudden onset of dyspnea and cyanosis twelve days before death. The second embolism resulted in death within a few minutes. From analysis of the case at necropsy, it seems most likely that the recent infarction of the myocardium occurred at the time of the first embolism, at which time the pulse rate rose to 160 and the respiratory rate to 50. No electrocardiogram was taken in this case.

CASE 4.—A 46 year old woman entered the clinic in October 1939, complaining of gradual abdominal distention and loss of weight. She had lost 15 pounds (6.8 Kg.) in the five weeks before entry.

The blood pressure was 120 mm. of mercury systolic and 80 diastolic. The heart was normal, and there was abdominal distention of grade 2 with shifting dulness. Abdominal exploration at this time revealed the presence of 4.5 liters of reddish straw-colored fluid and generalized peritonitis with considerable injection of the peritoneum. Inoculation of the fluid into guinea pigs gave negative results for tuberculosis, and biopsy of the omentum gave negative results for a malignant growth. On the seventh postoperative day the patient had right iliofemoral thrombophlebitis, which subsided without subsequent swelling. She received twelve roentgen treatments to the abdomen shortly after operation.

She returned in January 1941, complaining of shortness of breath, at which time she was found to have a pleural effusion on the left side. Diagnostic thoracentesis was performed, and the fluid on inoculation in guinea pigs proved to be negative for tuberculosis. The patient was given two roentgen treatments to the left side of the chest, and the effusion subsided.

In June 1941 she began to have intermittent bloody discharge from the vagina but otherwise remained in good health. On November 7 she was awakened at night by a severe pain in the left side of the chest which extended down the left arm. The pain lasted one hour, during which time she was dyspneic and after which she complained of weakness. Another similar episode occurred on November 13, and the patient entered the hospital on November 15 because of considerable shortness of breath on exertion.

The blood pressure was 140 mm. of mercury systolic and 86 diastolic. The chest revealed no abnormality. To the left of the sternum toward the apex of the heart a diastolic gallop rhythm was heard. The patient was moderately dyspneic, with moderate cyanosis and pallor of the lips. The electrocardiogram taken on November 18 showed that the chief initial ventricular deflection was normal in all three limb leads, with an elongated S wave in lead I, an inverted T wave in lead III and a notched QRS complex in lead III (fig. 4). No chest leads were taken.

The patient remained quite dyspneic and somewhat restless, with considerable relief of the dyspnea on breathing 100 per cent oxygen. The venous pressure measured 22 cm. of water on November 18. Later the same day a severe pain developed in the left lower anterior portion of the chest, followed by vomiting and profound shock. The blood pressure and the pulse were imperceptible, and the patient died thirty-five minutes later.

The anatomic diagnosis was (1) thrombosis of the right iliac vein with bilateral organizing emboli, (2) thrombosis of a small distal branch of the anterior descending coronary artery with acute and healing myocardial infarcts (1 to 2 cm. in diameter) at the apex of the left ventricle, (3) acute and healing myocardial infarcts of the interventricular septum in the region of the pulmonary conus, of multiple papillary muscles of the right ventricle, of the anterior papillary muscle of the left ventricle and of the posterior wall of the left ventricle and the interventricular septum, (4) dilatation of the right ventricle, grade 3, with mural thrombi, (5) polypoid carcinoma of the uterus with metastasis to the aortic lymph nodes and (6) chronic passive congestion of the liver with central necrosis.

The thrombus found in the branch of the left descending coronary artery only partially occluded the artery and was partially organized. The age of this thrombus and the surrounding early healing infarct of the myocardium (fig. 7*a*) was estimated at about twelve to fourteen days. No freshly thrombosed arteries were found to account for the adjacent acute infarction at the apex of the left ventricle or the acute and healing regions of infarction found in the other locations of the heart. Coronary sclerosis was equal throughout all the arteries and was grade 1. The right auricle was dilated (grade 2) and the right ventricle measured 0.5 cm. in spite of the considerable dilatation.

Even though thrombosis was found in one small branch of a coronary artery, case 4 is classified in this group since no thrombosis was found to account for the other regions of both acute and healing myocardial infarction which were observed. It will be noted also that the thrombus found in the branch of the left descending coronary artery only partially occluded the lumen. This region of healing infarction at the apex as well as the other smaller regions of healing infarction were thought to have occurred on November 7, at which time the patient apparently had a good-sized pulmonary embolus. The pain in the chest with extension down the left arm was probably due to the infarction of the heart that took place at that time. The more acute infarcts were estimated to be less than seven days old and probably

occurred during or after the episode noted on November 13, at which time the patient had another pulmonary embolism. The acute infarction was particularly remarkable in the interventricular septum in the region of the pulmonary conus (fig. 7 *b*) and the papillary muscles of the right ventricle, suggesting that decreased coronary arterial blood flow, as a result of greatly increased pressure in the right ventricle, was the cause of the infarction. The electrocardiogram was suggestive of a greatly increased strain on the right ventricle. Death in this case was apparently the result of failure of the right ventricle, since no embolism was found which was not partially organized to the pulmonary artery.

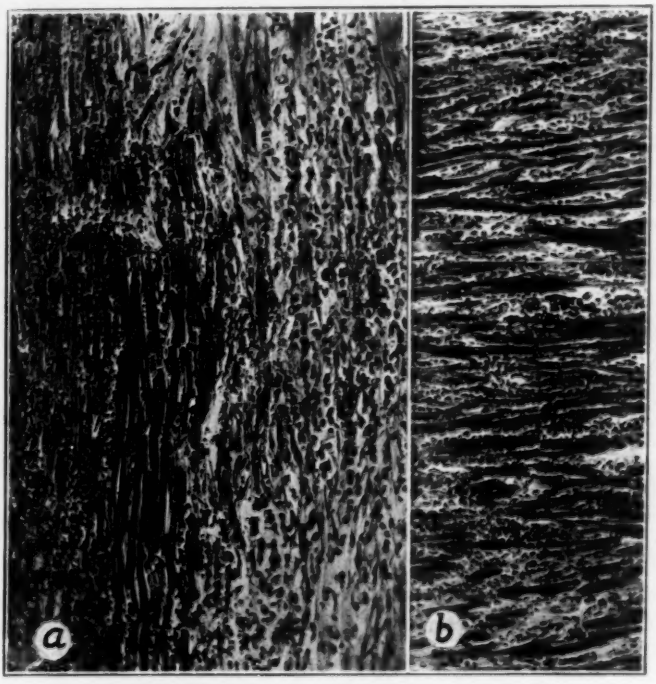

Fig. 7.—(*a*) Section from the region of acute infarction at the apex of the left ventricle. It reveals healing infarction on the right and acute infarction with hemorrhage on the left. (*b*) Section from the interventricular portion of the conus arteriosus, demonstrating acute infarction with many polymorphonuclear cells without hemorrhage. This infarction is quite extensive.

The history of the abdominal ascites, followed by pleural effusion, both responding to small doses of roentgen therapy, suggests that both were due to metastasis from the uterine carcinoma, which was quite radiosensitive. Inoculations of the fluid into guinea pigs gave negative results, and the only evidence of tuberculosis at necropsy was the presence of calcified hilar lymph nodes.

Myocardial Infarction with Coronary Occlusion.—One case was encountered in which the myocardial infarction was associated with recent thrombosis of the coronary artery.

Case 5.—A 53 year old man entered the hospital on Oct. 27, 1940, complaining of marked dyspnea and intermittent nocturnal dyspnea of one month's duration. Three years before entering,

he had had an episode of prolonged substernal pain lasting two days, which was considered to be due to coronary occlusion with myocardial infarction. Since that time his cardiac reserve had been decreased and he had noted angina on exertion. His blood pressure of 160 mm. of mercury systolic and 110 diastolic. The heart was enlarged on examination, and the liver was palpable 2 fingerbreadths below the right costal border. On November 2 the patient had a sudden onset of severe pain in the right upper quadrant of the abdomen, extending to the back. At this time he was nauseated and vomited. The edge of the liver was tender to palpation, and the pulse rate rose to 120. Two days later he complained of pleuritic pain in the left side of the chest and raised bright red sputum.

Hemoptysis continued, and a friction rub developed over the left lower posterior portion of the chest. The patient's condition remained unchanged until November 8; then, after intravenous administration of 300 cc. of a 20 per cent solution of dextrose, acute pulmonary edema developed, and he died six hours later. An electrocardiogram taken on November 8 revealed only left axis deviation, a depressed ST segment in lead I and an inverted T wave in lead I (fig. 4).

The anatomic diagnosis was (1) hypertrophy of the heart (620 Gm.) with dilatation of the left ventricle, (2) bilateral pulmonary embolism with organization, (3) multiple bilateral pulmonary infarctions with formation of an abscess in the lower lobe of the right lung, (4) coronary sclerosis, grade 2, with recent thrombosis of the right coronary artery, (5) patchy regions of recent myocardial infarction of the right ventricle, of the posterior wall of the left ventricle and of the interventricular septum and (6) myocardial scarring in the anterior portion of the interventricular septum.

The heart was enlarged and both the left ventricle and the left auricle were dilated (grade 2). There was considerable sclerosis (grade 3) of the left circumflex and right coronary arteries, and several branches of the left descending artery were occluded by arteriosclerosis.

It is difficult in case 5 to follow the exact course of events, but it is apparent that the patient had long-standing coronary and hypertensive heart disease which was complicated in the end stage by multiple pulmonary emboli. The episode of pain and tenderness in the right upper quadrant of the abdomen was undoubtedly a manifestation of pulmonary embolism of the lower lobe of the right lung with involvement of the pleura. It is probable that at the same time thrombosis of the right coronary artery developed, since the estimated age of this thrombosis was approximately one week. The myocardial infarctions in the right ventricle, the posterior wall of the left ventricle and the interventricular septum were also recent and corresponded approximately to the age of the thrombosis of the right coronary artery.

It is interesting to note that there was no recent infarction in the region of the scar in the lower two thirds of the anterior wall of the left ventricle and the interventricular septum, where one might expect the blood supply to be poor as a result of the previous coronary occlusion. The electrocardiogram taken on the day of death does not reveal evidence of either the recent injury to the heart or the result of the previous coronary thrombosis with myocardial scarring. The recent myocardial infarction was not extensive enough to alter the electrocardiogram appreciably, while the old scar was located mainly in the anterior portion of the interventricular septum, which seldom affects the electrocardiogram unless one or more of the conducting bundles are destroyed. Chest leads might have been of diagnostic aid in this case but unfortunately were not obtained.

Myocardial Infarction of the Posterior Wall of the Left Ventricle Resulting from Severe Prolonged Shock.—This case is presented as an illustration of what may occur in the heart as a result of severe prolonged shock without occlusion of a coronary artery.

CASE 6.—A 54 year old man entered the hospital on March 9, 1941, complaining of recurrent chills and fever of three months' duration. The patient stated that for two weeks in January 1940 he had been quite hoarse, but that after this he was well until three months before entry, when recurrent episodes of chills and fever developed, with a rise of temperature to 104 F. He

had a slight cough during this time and raised small amounts of yellow-colored sputum. During the three months he had lost 40 pounds (18 Kg.).

The patient was well developed but appeared chronically ill and was sweating moderately. His blood pressure was 130 mm. of mercury systolic and 80 diastolic, his pulse rate 68 and his respiratory rate 20. There were dulness to percussion and decreased breath sounds over the entire chest, especially the lower half. The cardiac rhythm was regular, and there was a grade 2 systolic murmur at the apical and the aortic areas of the heart. A roentgenogram of the chest revealed complete opacity of the entire left side of the chest with a shift of the heart and the mediastinum to the left. A roentgenogram of the chest taken with the use of a Bucky diaphragm revealed a tumor mass in the left upper part of the chest, extending to the level of the ninth rib posteriorly, and elevation of the left side of the diaphragm. The concentration of hemoglobin was 10.2 Gm. per hundred cubic centimeters of blood. The serologic reaction for syphilis was 4 plus. Bronchoscopic examination on three occasions revealed a large tumor mass which almost completely obstructed the left main bronchus, located at the bifurcation of the left upper and the left lower bronchus. Biopsy revealed only inflammatory tissue.

On the evening of April 6 the patient fainted after straining at stool; the pulse rate rose to 120, and the blood pressure was 100 mm. of mercury systolic and 70 diastolic. On the following morning he passed a tarry stool. At 9 p. m. on April 7 the patient suddenly became semicomatose and pale, with a pulse rate of 154, and the blood pressure was unobtainable. Shortly thereafter he passed a large bloody stool involuntarily. The patient remained irrational, his skin was pale and cyanotic, and his blood pressure remained imperceptible. His pulse rate ranged from 120 to 160. He was given three blood transfusions without improvement and died fifty-four hours after the onset of shock.

The anatomic diagnosis was (1) syphilitic aortitis with aneurysmal formation of the arch of the aorta and extension of the aneurysm into the esophagus and the left main bronchus, (2) rupture of the aneurysm into the esophagus with gastrointestinal hemorrhage (2,000 cc.), (3) atelectasis of the upper lobe of the left lung with bronchiectasis, (4) hypertrophy of the heart (510 Gm.), (5) acute infarction of the posterior wall of the left ventricle in the middle third, measuring 2 by 1.5 cm., and of the posterior papillary muscle (fig. 8 *a* and *b*).

The coronary sclerosis was minimal and was graded accordingly: (1) left descending artery, grade 1; (2) left circumflex artery, grade 1; (3) right coronary artery, grade 2. The orifice of the right coronary artery measured 2 by 2.5 mm. and was thought to be narrowed slightly by the syphilitic process of the aorta. The right coronary artery supplied the posterior wall of the left ventricle in the region in which the acute infarction was found.

Case 6 illustrates what may happen in the heart as a result of severe, prolonged shock. Two factors should be considered: (1) the decreased coronary arterial flow as a result of the great drop of blood pressure, both systolic and diastolic, and (2) the definite anoxia, evidenced by the persistent cyanosis in the presence of moderate anemia.

Pulmonary Embolism with Electrocardiographic Changes but Without Myocardial Infarction.—These cases are presented to illustrate the large group of cases in which, despite pulmonary embolism, no anatomic changes could be demonstrated in the myocardium. In the first case infarction of the posterior wall of the left ventricle was diagnosed clinically, chiefly by the electrocardiographic limb leads. In the second case the clinical picture was suggestive of pulmonary embolism and the electrocardiographic chest leads confirmed the diagnosis.

Case 7.—A 66 year old laborer entered the hospital on Aug. 25, 1939 because of two recent episodes of pain in the chest and dyspnea. On August 11 he had walked to the bathroom at 4 a. m., and while sitting on the stool, suddenly lost consciousness and was unconscious eight to ten minutes. On regaining consciousness, he was severely dyspneic and was sweating profusely but was able to return to his bed. Two days later, after a large evening meal, he suddenly became faint, and a bandlike pain developed across the lower part of the chest. He was dyspneic and perspired a good deal. The pain subsided in a few minutes.

On August 22 he had experienced a second episode of pain in the chest with sweating and dyspnea.

He was a well developed, slightly obese man. His blood pressure was 132 mm. of mercury systolic and 76 diastolic. His chest was clear, the heart sounds were distant but normal, and the pulse rate was 90.

On the night of August 30, the patient awoke with a steady epigastric pain associated with dyspnea and sweating, which was relieved by glyceryl trinitrate. On the following morning the same pain occurred after eating, and for the third time the same evening, at which time the pain was relieved again by glyceryl trinitrate. On September 1 the patient became extremely dyspneic and sweated profusely. Severe shock developed, with blood pressure and pulse imperceptible. He died twenty-five minutes after the onset of this final episode.

Four electrocardiograms were taken, which were similar. There was an imperfect Q wave–T wave pattern in lead III with inversion of the T wave in lead IV R and an abnormally positive T wave in the Wolferth lead (fig. 9). The clinical diagnosis was considered to be myocardial infarction of the posterior wall of the left ventricle.

The anatomic diagnosis was (1) fatal pulmonary embolism, (2) hypertrophy of the heart (420 Gm.).

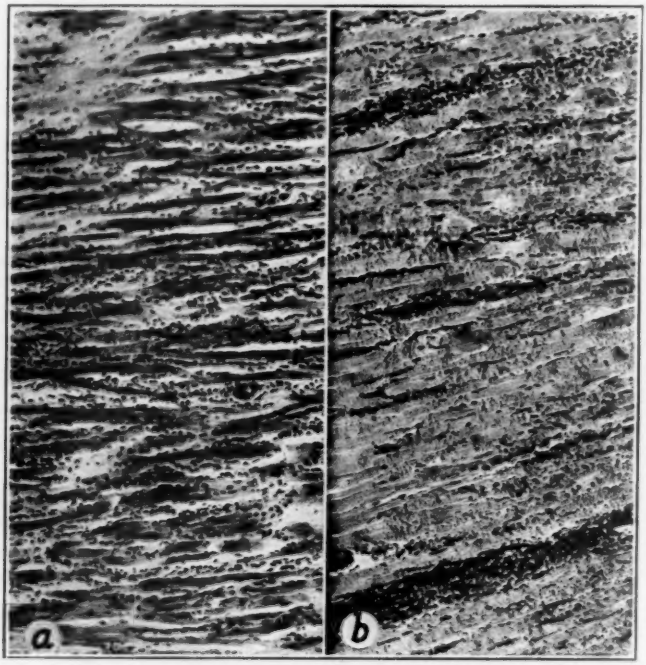

Fig. 8.—(*a*) Section from the posterior papillary muscle close to the tip demonstrating acute infarction; (*b*) region of acute infarction from the midportion of the posterior left ventricle adjacent to the interventricular septum. Regions of moderate hemorrhage and dilatation of the blood vessels are present.

Both the right auricle and the right ventricle were dilated (grade 3), and the thickness of the wall of the right ventricle averaged 0.7 cm. The thickness of the wall of the left ventricle measured 1.7 cm. The coronary sclerosis was graded 1, and no thrombi were found in the coronary arteries. Numerous sections of the myocardium, especially of the posterior wall of the left ventricle, were made and did not reveal any evidence of infarction.

Case 7 illustrates the pitfalls in distinguishing between pulmonary embolism and myocardial infarction of the posterior wall of the left ventricle in certain cases. Significant changes are demonstrable in the electrocardiographic limb leads and chest leads without morphologic change in the heart muscle. At the same time it is of interest to note that on three different occasions the patient was relieved of anginal pain by glyceryl trinitrate (Scherf). In view of the absence of significant coronary

sclerosis found at necropsy, the relief of pain in the chest afforded by the administration of glyceryl trinitrate suggests that the coronary blood flow had been diminished by spasm. If such an assumption should be correct, it would support the thought of some investigators that spasm of the coronary arteries may occur in conjunction with pulmonary embolism.

Case 8.—A 57 year old farmer was brought to the hospital on Nov. 28, 1940, having been unconscious for two hours after an automobile accident. Soon after entry he underwent an

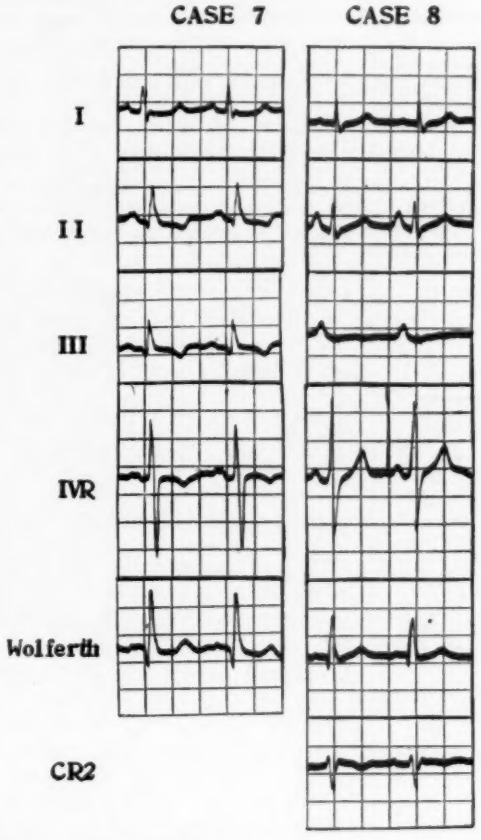

Fig. 9.—Case 7. The electrocardiogram, taken on Aug. 31, 1939, shows an imperfect Q wave–T wave pattern in lead III with a slight prolongation of ST. The chest leads are particularly interesting since the T waves in the apical and Wolferth leads are the reverse of normal.

Case 8.—The electrocardiogram, taken on Dec. 24, 1940, reveals prominent P waves in leads II and III, a small ST and an isoelectric T. The chest leads are diagnostic of pulmonary embolism with a normal T wave in lead IV R and T waves in the CR_2 and Wolferth leads the reverse of normal.

operation for decompression and elevation of a skull fracture. He responded well, and the course of his recovery was uneventful until December 14, when he complained of pleurisy in the right lower portion of the chest, and his temperature rose to 99.6 F. This subsided in two days, and he was dismissed from the hospital on December 21 to stay in a convalescent home.

On December 24, while walking about, he was seized with sudden weakness and vomiting but did not lose consciousness.

When examined, one hour later, he showed moderate cyanosis; the extremities were cold, the skin was moist and the blood pressure was 80 mm. of mercury systolic and 40 diastolic. The pulse rate was regular at 120, and the respiratory rate was 40. The patient complained of moderate substernal pain. Oxygen (100 per cent) was administered, and the patient gradually improved so that after ten hours the pulse rate was 110, the blood pressure 100 systolic and 70 diastolic, and the respiratory rate 28. The electrocardiogram taken on December 24 revealed exaggerated P waves in leads II and III, shallow inversion of the T wave in lead III, an inverted T wave in lead CR_2 and an abnormally positive T wave in the Wolferth lead (fig. 9).

The patient improved after this episode, but on Jan. 2, 1941 he had a gradual rise of temperature to 102 F. with a concomitant rise of the pulse rate to 110 and of the respiratory rate to 30, during which time the pain in the right side of the chest returned. His condition again improved, and he was prepared for dismissal when, on January 8, while being bathed, he suddenly became weak and dyspneic, vomited, complained of pain in the lower anterior portion of the chest and died within an hour.

The anatomic diagnosis was (1) bilateral fatal pulmonary embolism with pulmonary infarction (source undetermined) and (2) hydrothorax on the right (400 cc.).

The heart weighed 305 Gm. The right ventricle was dilated (grade 3), and the wall measured 5 mm. in thickness. The coronary arteries were patent throughout, and the sclerosis was grade 1. Sections of the heart failed to reveal any regions of acute or healing infarction. In the inferior vena cava, a medium-sized clot was found lying loosely at the level of the renal vein but without attachment to the wall.

Case 8 well illustrates the diagnostic value of the electrocardiographic leads from the chest in pulmonary embolism. The leads from the limbs by themselves were of little value in corroborating the clinical impression of pulmonary embolism, although the exaggeration of P waves in leads II and III might be suggestive. However, the T waves in the CR_2 and Wolferth leads are the reverse of normal and under these circumstances are diagnostic of pulmonary embolism. It will be noted also that these changes take place, as in case 7, in the absence of demonstrable anatomic alterations of the myocardium.

GENERAL COMMENT

The role that reflex factors resulting from embolism in the pulmonary artery may play in the clinical picture of pulmonary embolism has received considerable comment in recent years. Some writers, particularly Leriche and de Takáts, have expressed the belief that in many cases the reflex factors play a major role and that, in fact, they are the cause of death in from 20 to 30 per cent of cases. These are cases in which at necropsy there are only small emboli in the pulmonary artery. Daly and his associates [22] demonstrated in dogs that a small but definite fall of the systemic arterial pressure accompanies a rise of the pulmonary arterial pressure, with a concomitant increase or decrease of the heart rate. A definite increase of the respiratory rate with embolism of the small pulmonary arterioles produced with particulate matter had been noted already, but this finding is difficult to translate into the clinical picture in which the embolizing clots are considerably larger. The reflex changes just mentioned disappear after the vagus nerves are sectioned. The observations by Scherf and Schönbrunner regarding the electrocardiographic changes in experimental pulmonary embolism seem insufficient alone to establish the occurrence of a pulmonocoronary reflex.

The recent observations by Megibow, Katz and Steinitz [23] concerning the dynamics of experimental pulmonary embolism again suggest that dynamic factors

22. Daly, I. de B.; Ludány, G.; Todd, A., and Verney, E. B.; Sensory Receptors in the Pulmonary Vascular Bed, Quart. J. Exper. Physiol. **27**:123-146, (Aug.) 1937.

23. Megibow, R. S.; Katz, L. N., and Steinitz, F. S.: Dynamic Changes in Experimental Pulmonary Embolism, Surgery **11**:19-32 (Jan.) 1942.

are sufficient to account for the death of animals. Using large, medium-sized and particulate matter to produce embolism in dogs, these investigators were able to account for death by the rise of pulmonary arterial systolic and diastolic pressure with resultant right ventricular heart failure. Cardiac arrhythmias are known to accompany pulmonary embolism both clinically and in the experimental field. They consist of auricular flutter, auricular fibrillation and terminal ventricular fibrillation in animals [24] and are the end result of failure of the right ventricle. Sudden death from pulmonary embolism, even though the embolism is relatively small, is best explained by the same mechanism of cardiac arrhythmia, probably resulting in ventricular fibrillation.

The occasional patient encountered clinically in whom angina pectoris develops after an attack of pulmonary embolism and is relieved by glyceryl trinitrate, as in case 7, is cited[12a] as giving evidence in favor of a reflex on the coronary arteries. However, there are undoubtedly other factors which affect coronary blood flow, such as fall of arterial pressure, which usually is associated with an increase of heart rate. The rise of pressure in the right auricle also increases the pressure in the coronary sinus, and this increase decreases the pressure gradient in the coronary arteries. The third contributing factor is the decrease of blood flow to the muscle of the right ventricle since, as Katz, Jochim and Weinstein [25] pointed out and as Visscher [26] emphasized, the major portion (92 per cent) of the venous return from the right ventricular wall empties into the right ventricle via the thebesian veins. Thus increase of pressure in the right ventricle decreases appreciably the coronary flow to this side of the heart. All these factors combine to impair the function of the right ventricle. The combined effect of increased work of the right ventricle and decreased coronary blood flow may account for the angina pectoris without the necessity of postulating a pulmonocoronary reflex to account for it.

That anatomic changes of the myocardium occur after pulmonary embolism has been demonstrated in recent publications.[27] Those changes in the myocardium are not often demonstrable, as is illustrated by the finding of only 5 cases in a total of 30 cases in this somewhat selective series. The fact that in 4 of these 5 cases no significant obstruction was found in the coronary arteries to account for acute infarction suggests that another factor, probably shock, contributes a great deal to the decrease of coronary blood flow. As far as infarction in the right ventricle is concerned, the rise of right intraventricular pressure also has the effect of decreasing coronary blood flow by decreasing the pressure gradient in the coronary artery, as pointed out in the preceding paragraph. Blumgart, Schlesinger and Zoll [28] have called attention to the fact that shock seems to predispose to coronary arterial thrombosis, and this is illustrated by case 5 of the present series. That profound shock alone can account for acute myocardial infarction is demonstrated clearly by case 6. It is interesting to note that in this case the infarction was located in that portion of the posterior left ventricular wall supplied by the right coronary artery, and this was predominantly true in cases 1, 2 and 5 of the cases presented.

24. Frommel, E.: Les troubles du rythme cardiaque au cours de l'embolie pulmonaire mortelle: Étude électrocardiographique expérimentale, J. de physiol. et de path. gén. **26**:247-249 (June) 1928.

25. Katz, L. N.; Jochim, K., and Weinstein, W.: The Distribution of the Coronary Blood Flow, Am. J. Physiol. **122**:252-261 (April) 1938.

26. Visscher, M. B.: The Restriction of the Coronary Flow as a General Factor in Heart Failure, J. A. M. A. **113**:987-990 (Sept. 9) 1939.

27. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675-1679 (April 29) 1939.

28. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock, Arch. Int. Med. **68**:181-198 (Aug.) 1941.

Electrocardiographic tracings were not obtained in all the cases in this series, so that it is impossible to determine the incidence of various types of changes in the electrocardiograms. Sokolow, Katz and Muscovitz [29] studied 50 cases of pulmonary embolism and noted only 5 with all of the changes delineated by McGinn and White. However, in 36 cases some of the electrocardiographic features of pulmonary embolism were present and could be termed suggestive of pulmonary embolism. In this regard Barnes [30] and Wood [31] directed attention to the value of the chest leads in the diagnosis of pulmonary embolism. Cases 7 and 8 illustrate well the value of these leads, especially the Wolferth lead.

As pointed out previously, the anatomic changes of acute infarction of the myocardium are infrequent in patients dying of pulmonary embolism. It is obvious, therefore, that the electrocardiographic changes known to indicate pulmonary embolism seldom if ever can be explained on that basis. Cases are presented (7 and 8) in which the electrocardiograms were characteristic of pulmonary embolism but in which no demonstrable anatomic change of the myocardium was found after careful search. Case 1 illustrates the electrocardiographic picture which may result if myocardial infarction occurs in the posterior portion of the right or the left ventricles after an attack of pulmonary embolism. In general, the strain placed on the right ventricle by pulmonary embolism seems to be the dominant factor in the production of the electrocardiographic picture. When shock is present a decrease of the coronary blood flow to the right side of the heart undoubtedly occurs. In the right ventricle this factor plus strain is complicated by a decrease of coronary blood flow to the right ventricle, resulting from a fall of the pressure gradient in the arteries supplying it. If these conditions are prolonged, marked dilatation occurs and scattered regions of acute infarction of the right ventricle can be demonstrated at times.

SUMMARY

A study of the heart was made in cases in which pulmonary embolism occurred. It is noted that the size of the heart in the surgical group of cases in which pulmonary embolism develops and the surgical group in which pulmonary embolism does not develop is essentially the same. Since chronic valvular defects and disease of the pericardium were excluded as causes of cardiac enlargement, this evidence indicates that hypertension does not predispose to pulmonary embolism among surgical patients. The heart was examined in 30 cases in which pulmonary embolism occurred, and evidence of acute infarction was found in 5. In 4 of these cases, no significant obstruction was found in the coronary arteries, but in the fifth case there was fresh coronary thrombosis. One case in which there was prolonged shock is presented. In this case there was acute infarction involving the posterior wall of the left ventricle, without coronary thrombosis. The electrocardiographic differentiation of infarction of the posterior wall of the left ventricle and pulmonary embolism is illustrated and discussed, and the value of the chest leads in differentiating the two is stressed. The mechanism of the production of electrocardiographic changes is discussed and a possible explanation for angina pectoris, which occasionally occurs in pulmonary embolism, is suggested.

102 Second Avenue, S.W.

29. Sokolow, M.; Katz, L. N., and Muscovitz, A. N.: The Electrocardiogram in Pulmonary Embolism, Am. Heart J. **19**:166-184 (Feb.) 1940.

30. Barnes, A. R.: Electrocardiographic Patterns: Their Diagnostic and Clinical Significance, Springfield, Ill., Charles C Thomas, Publisher, 1940.

31. Wood, P.: Pulmonary Embolism: Diagnosis by Chest Lead Electrocardiography, Brit. Heart J. **3**:21-29 (Jan.) 1941.

CLINICAL EFFECTIVENESS AND SAFETY OF A NEW SYNTHETIC ANALGESIC DRUG, DEMEROL

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Since March 1941 I have had the opportunity to investigate a new synthetic analgesic drug, demerol,[1] for the treatment of pain due to a variety of medical and surgical conditions. A year's experience has definitely indicated its value as an analgesic agent, and it was therefore deemed advisable to report on its effectiveness, potency and safety. In addition, its pharmacologic action in man relative to a comparison with morphine will be considered briefly.

Eisleb and Schaumann [2] introduced the drug in 1939 in an effort to obtain a synthetic substitute for atropine. However, it was soon noted on pharmacologic grounds that in addition to a slight atropine-like action on all smooth muscle, the drug possessed the unexpected effect of a morphine-like response on the central nervous system. Extensive pharmacologic and toxicologic studies have since been reported by Duguid and Heathcote [3]; Schaumann [4]; Gruber, Hart and Gruber,[5] and Barlow.[6] With the exception of Gruber and his co-workers, who noted a spasmodic action of demerol on all smooth muscle, all investigators have reported an antispasmodic action attributable to a depression of the parasympathetic nerve endings and of smooth muscle directly. The former action resembled that of atropine but was not as marked, while the direct muscular depression was greater than that produced by papaverine. After careful experiments on animals and on human subjects, particularly on the latter, Barlow,[7] using the Hardy, Wolff and Goodell [8]

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1. The Alba Pharmaceutical Company, Inc., supplied us with the drug and with other aid in connection with this investigation.

2. Eisleb, O., and Schaumann, O.: Dolantin, ein neuartiges Spasmolytikum und Analgetikum (Chemisches und Pharmakologisches), Deutsche med. Wchnschr. **65**:967 (June 16) 1939.

3. Duguid, A. M. E., and Heathcote, R. St. A.: Pharmacological Action of Ethyl Methylphenylpiperidine Carboxylate, Quart. J. Pharm. & Pharmacol. **13**:318 (Oct.-Dec.) 1940.

4. Schaumann, O.: Ueber eine neue Klasse von Verbindungen mit spasmolytischer und zentral analgetischer Wirksamkeit unter besonderer Berücksichtigung des 1-Methyl-4-Phenyl-Piperidine-4-Carbonsaüre Äthylesters (Dolantin), Arch. f. exper. Path. u. Pharmakol. **196**: 109, 1940.

5. Gruber, C. M.; Hart, E. R., and Gruber, C. M., Jr.: The Pharmacology and Toxicology of the Ethyl Ester of 1-Methyl-4-Phenyl-Piperidine-4-Carboxylic Acid (Demerol), J. Pharmacol. & Exper. Therap. **73**:319 (Nov.) 1941.

6. Barlow, O. W.: Studies on Pharmacology of 1-Methyl-4-Phenylpiperidin-4-Carbonic Acid Ethylester (D-140, Demerol): II. Pharmacology, Toxicology, and Addiction Liability, to be published.

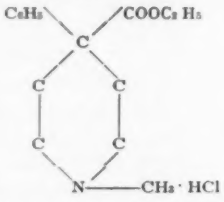
7. Barlow, O. W.: Studies on the Pharmacology of 1-Methyl-4-Phenylpiperidine-4-Carbonic Acid Ethyl Ester (D-140, Demerol): I. Analgesic Action, to be published.

8. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: A New Method for Measuring Pain Threshold; Observations on Spatial Summation of Pain, J. Clin. Investigation **19**:649, 1940.

technic, concluded that in analgesic potency demerol was intermediate between codeine and morphine.

Since 1939 numerous clinical reports have appeared attesting to the drug's effectiveness in relief of pain due to a variety of conditions. Its use for postoperative pain and other surgical conditions was described by Dolle,[9] Rosenthal,[10] Schäfer,[11] Schlungbaum [12] and Sostmann.[13] Medical conditions, including arthritic, neurologic and colicky pains of all organs and causations, were reported by Althoff,[14] Dietrich,[15] Klein,[16] Reisinger [17] and Heydner.[18] The consensus was that demerol [19] was a safe analgesic approximating the effectiveness of morphine for the relief of pain.

Demerol is 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester hydrochloride and has the following structural formula:



It differs from morphine in that it is relatively simple and does not contain the phenolic and alcoholic hydroxyl groups attached to a phenanthrene nucleus to which the properties of morphine have been attributed. However, on close inspection of the morphine structure a piperidine ring can be made out if the ethenamine chain attached to the phenanthrene nucleus is rearranged. Atropine also possesses a piperidine ring, but this is included in the tropine nucleus.

SCOPE OF INVESTIGATION AND SELECTION OF PATIENTS

During the period of investigation, from March 1941 through April 1942, demerol was used in an effort to control or abolish the pain associated with a large variety of medical and surgical conditions. Patients admitted to the medical and surgical wards of the Third Medical Division [20] (New York University), Bellevue

9. Dolle, W.: Dolantin, ein neues Spasmolyticum und Analgeticum in der Gynäkologie, Prakt. Arzt **25**:113, 1940.

10. Rosenthal, H.: Beobachtungen zur Bekampfung des Wundschmerzes mit dem neuen Analgetikum, Dolantin, München. med. Wchnschr. **86**:1079 (July 14) 1939.

11. Schäfer, F.: Schmerzbekampfung in der Chirurgie mit Dolantin, Deutsche med. Wchnschr. **65**:970 (June 16) 1939.

12. Schlungbaum, H.: Schmerz Bekämpfung mit Dolantin, einem synthetisch hergestellten Spasmolytikum und Analgetikum, Med. Klin. **35**:1259 (Sept. 22) 1939.

13. Sostmann, H. E.: Zur Ablösung des Morfins und seiner Abkömmlinge in der Gynekologie durch Dolantin, Med. Welt **14**:325 (March 30) 1940.

14. Althoff, H.: Klinische Erfahrungen mit Dolantin-Bayer, Therap. d. Gegenw. **6**:258, 1939.

15. Dietrich, H.: Klinische Erfahrungen mit einem neuen synthetischen Spasmolytikum und Analgetikum, Deutsche med. Wchnschr. **65**:969 (June 16) 1939.

16. Klein, E. K.: Erfahrungen mit Dolantin, einem Myotrop und Neurotrop wirkenden Spasmolytikum, München. med. Wchnschr. **86**:1674 (Nov. 24) 1939.

17. Reisinger, F.: Das neue Analgetikum und Spasmolyticum Dolantin, Wien. med. Wchnschr. **90**:400, 1940.

18. Heydner, W.: Erfahrung mit dem Spasmo-Analgetikum Dolantin bei Nervkranken, Fortschr. d. Therap. **16**:33, 1940.

19. Demerol was introduced in Europe as "eudolat" and was subsequently known on that continent and in South America as "dolantin."

20. Dr. William S. Tillett, Director of the Third Medical Division, and Dr. John H. Mulholland, Director of the Third Surgical Division, furnished clinical material for this study.

Hospital, were utilized for this purpose. Demerol was given to any patient presenting pain regardless of its causation, type, severity or duration or the organ involved. The age and sex of the patient and accompanying conditions were not factors for selection. Consciousness and cooperativeness were the main considerations, since subjective responses were essential for evaluation of effectiveness and untoward reactions.

The scope of the investigation is presented in table 1. Of the 1,220 patients to whom demerol was administered, 1,119 were included in the final analysis. The others were discarded because they may have received other medication at the same time or because their mental state made it impossible to obtain adequate subjective data. There are 462 female and 657 male patients, ranging in age from 13 to 92 years. The records of 136 ambulatory patients [21] have been included only for a

TABLE 1.—*Scope of the Investigation on Demerol*

		Number of Patients
Hospitalized patients	Females	462
	Males	657
	Total	1,119
Ambulatory patients		136
Age	13 to 92	
Surgical conditions	Postoperative	418
	Nonoperative	406
	Total	824
Medical conditions		406
Dose (parenteral and oral)	50 to 200 mg.	
Patients receiving demerol	Parenterally only	436
	Orally only	300
	Parenterally and orally both	383
	Total	1,119
Period of administration of demerol, days		
7 or less		805
8 to 14		158
15 to 30		96
31 to 60		43
61 to 90		13
Over 90		4
Total		1,119
Doses administered to hospitalized patients	Parenteral	10,320
	Oral	10,581

comparative analysis with those of the hospitalized patients for untoward reactions. The effectiveness of demerol in this group will not be considered at the present time.

Several additional groups of patients have received demerol for purposes other than the relief of pain. Investigation is now in progress regarding the use of demerol (1) as a sedative or soporific, (2) in the treatment of bronchial asthma, (3) in the relief of the acute dyspnea of congestive heart failure, (4) in the treatment of addiction to opiates and (5) as an analgesic agent in obstetrics. Rovenstine and Batterman [22] are reporting on its use as a substitute for morphine as a preanesthetic agent.

21. Ambulatory patients were made available for study by Dr. Currier McEwen, Chief of the Arthritis Clinic; Dr. Robert P. Wallace, Chief of the Gastroenterology Clinic; Dr. Aaron Brown, chief of the Asthma Clinic, and Dr. Rieva Rosh, chief of the Radiation Clinic, all of the Third Medical Division (New York University), Bellevue Hospital.

22. Rovenstine, E. A., and Batterman, R. C.: The Utility of Demerol as a Substitute for the Opiates in Pre-Anesthetic Medication, Anesthesiology, to be published.

Demerol was used in the treatment of pain due to surgical conditions in 824 patients and to medical conditions in 406 patients. If a patient presented more than one type of pain at the same or at different times he was included for evaluation of effectiveness in the appropriate groups of diagnoses. For example, a patient may have been treated for pyloric spasm and therefore included in the medical group. However, if surgical intervention was performed on the same patient, he was also included under postoperative pain in the surgical group.

The drug [23] was administered in doses of 50 to 200 mg. in a single dose or in repeated doses several times daily. Different doses or routes of administration may have been used in the same patient. It was thus given only parenterally (intramuscularly or subcutaneously) to 436 patients, only orally to 300 patients and by both methods at different times to 383 patients. The majority of the patients received the drug for less than one week, but in 60 patients it was possible to study its effects for over a month. Over ten thousand injections and a similar number of oral doses were administered to the hospitalized patients, 11 patients receiving more than 20,000 mg. of the compound.

RESULTS

After the oral administration of demerol an analgesic effect is apparent within twenty to sixty minutes, and after parenteral administration, within fifteen minutes. In either case the analgesia lasts from one to several hours, with an average duration of three hours. As in the case of other analgesics, the more severe the pain, the shorter the duration of action. Pain of visceral origin is relieved for longer periods than pain arising from skeletal or neurologic structures. The intensity and the duration of the effect, in contrast to those of morphine and codeine, were not influenced by the presence of anemia or advanced disease of the liver, kidneys or heart.

In evaluating the effectiveness of demerol several factors were taken into consideration. It must be emphasized that one is dealing with a symptomatic measure and not a specific cure. An analgesic agent offers only a means of controlling the pain, thus making the patient comfortable while the specific cause of his complaints is discovered and eradicated. This aspect is often overlooked, and when assessing an analgesic drug one finds, particularly if the medication is given only occasionally, that the patient may continue to have pain. On close questioning, however, one may discover that there was complete relief of pain for the duration of the drug's action, but when the effect is dissipated, the patient considers himself unrelieved. Therefore, the principal factors considered in my analysis were the degree and the duration of relief of pain, dependent on the type of pain; the dose of drug administered; the rapidity of dissipation of the drug from the body, and the psychologic makeup of the patient. The last is of prime importance, since much of my data is obtained by close questioning of the patient.

With this in mind the effectiveness of demerol was divided into four categories:

1. Complete control of pain, including complete relief of pain for three or more hours and almost complete relief of pain for several hours. In this group untoward reactions were minimal or entirely absent.

2. Moderate control of pain, including complete relief and almost complete relief of pain for under three hours, partial relief for three hours or more and relief as described in the first category if untoward reactions were disturbing and did not permit complete comfort.

23. Demerol was supplied in 50 mg. tablets under the research number D-140 and in solution, research number S-140, either in an ampule or in a vial so that 1 cc. was equivalent to 50 mg.

TABLE 2.—*Effectiveness of Demerol in Terms of Dose, Administered Both Parenterally and Orally, Regardless of Diagnosis or Severity of Pain*

Dose, Mg.	Effectiveness																
	Administered Parenterally*									Administered Orally*							
	No. of Trials†	Complete		Moderate		Slight		None		No. of Trials†	Complete		Moderate		Slight		None	
		No.	%	No.	%	No.	%	No.	%		No.	%	No.	%	No.	%	No.	%
50	83	56	67.4	19	22.9	6	7.2	2	2.4	235	128	54.4	48	20.4	32	13.6	27	11.5
75	222	182	81.9	29	13.0	7	3.1	4	1.8	39	18	46.1	11	28.2	7	17.9	3	7.7
100	643	569	88.4	54	8.4	9	1.4	11	1.7	431	284	65.9	103	23.9	21	4.9	23	5.3
150	40	34	85.0	4	10.0	..	...	2	5.0	14	6	42.9	8	57.1	..	...	..	...
200	8	8	100	..	....	..	...	..	...	3	1	....	2	....	..	...	..	...
Total.....	996	849	85.2	106	10.6	22	2.2	19	1.9	722	437	60.5	172	23.8	60	8.3	53	7.3

* Different doses and methods of administration may have been used on the same patient.
† Number of trials of demerol possible of evaluation.

3. Slight control of pain, including partial relief for under three hours and relief as described in the first and the second category if untoward reactions were moderately severe.

4. No control of pain, including failure to affect pain and relief as described in the first three categories if untoward reactions were severe.

The effectiveness in terms of dose, both parenteral and oral, regardless of diagnosis, is summarized in table 2. With increasing dose a higher incidence of complete control of pain is obtained. For the average patient 100 mg. of demerol is a satisfactory dose. Such a dose resulted in a good effect in 88 per cent of the trials after parenteral administration and 66 per cent after oral administration. The latter method of administration gives an effect equivalent to one obtained with 50 mg. given intramuscularly. In many instances in which an opportunity presented itself for a comparison with morphine, it was apparent that 100 mg. of demerol given intramuscularly was equivalent to 10 mg. of morphine. However, the duration of action was not as long.

From table 3 it will be noted that regardless of causation and severity of the pain, completely satisfactory results were achieved in 85 per cent of the 997 trials in 881 of the patients to whom demerol was administered parenterally and in 60 per

TABLE 3.—*Effectiveness of Demerol in Each Group of Patients Treated, Parenterally and Orally, Regardless of Dose*

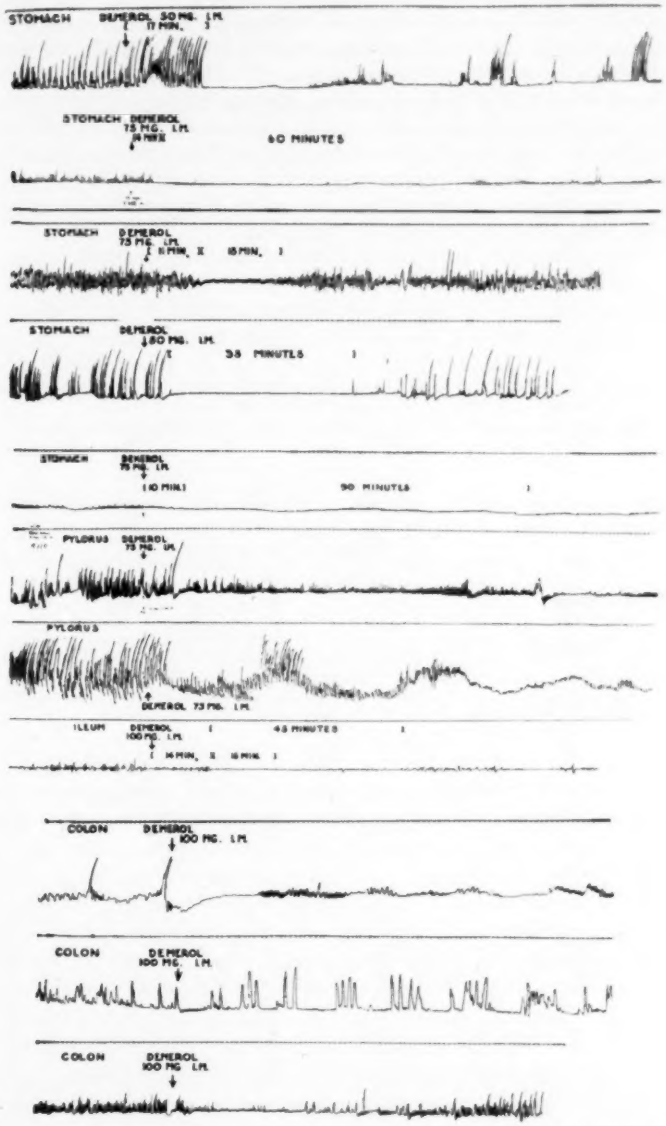
Diagnosis	Method of Administration of Demerol	No. of Patients	No. of Trials	Effectiveness, Percentage of Patients			
				Complete	Moderate	Slight	None
Postoperative pain	Parenteral	302	386	93.0	4.1	1.5	1.5
	Oral	96	101	88.1	8.9	...	2.9
Nonoperative surgical conditions	Parenteral	265	317	81.4	14.8	2.5	1.2
	Oral	255	316	64.8	23.1	6.0	6.0
Medical conditions	Parenteral	254	293	79.5	14.6	2.7	3.0
	Oral	253	305	46.9	29.5	13.4	10.2
All diagnoses	Parenteral	881	996	85.2	10.6	2.2	1.9
	Oral	604	722	60.5	23.8	8.3	7.3

cent of the 722 trials in 604 patients to whom it was given orally. If the patients in whom the drug was moderately effective are included, satisfactory control of pain was achieved in 96 per cent and 84 per cent, respectively, with parenteral and oral routes of administration.

The most satisfactory results were obtained in the group of patients treated postoperatively. The postoperative course following major surgical procedures, such as laparotomy, thyroidectomy, mastectomy and herniorraphy, is well controlled, with a minimum of untoward reactions. Here more than in any other group of patients may the results be considered on an objective basis, since for the first twenty-four hours after operation the patient is still under the influence of the anesthetic, and one must rely entirely on direct observation. The immediate relief of restlessness, the rapidity with which the patient becomes comfortable and the minimal distress produced by the usual postoperative therapeutic procedures are all striking objective evidence for the effectiveness of demerol under such circumstances.

In the treatment of nonoperative surgical conditions the parenteral use of the drug was found to be effective for skeletal pain associated with fractures and metastatic malignant growths, arterial occlusions, impending gangrene, thrombophlebitis, pleuritic pain of fractured ribs and nonspecific pain associated with various malignant growths. Although the oral use of demerol is less effective in this group, the pain may be satisfactorily controlled if an appropriate dose is given.

For all medical conditions demerol administered parenterally was completely effective in 80 per cent of the trials and moderately effective in an additional 15 per cent. Although in 76 per cent of the trials a moderately to completely satisfactory



Representative tracings made on 11 subjects after intubation studies with balloons in various portions of the gastrointestinal tract, showing the antispasmodic action of demerol administered parenterally.

response was obtained with the orally administered preparation, the relief of pain is less rapid and less dramatic than after injection. By all methods of administra-

tion excellent results are obtained in pleuritic pain regardless of causation; pain in neurologic conditions, such as sciatica, tabes dorsalis and radiculitis; cardiovascular pain, such as that associated with a severe anginal syndrome and the distress of congestive heart failure, and visceral or colicky pain of biliary, renal and gastrointestinal origin. The last is of particular interest, since the antispasmodic action of demerol contributes to its analgesic properties. In 27 human subjects direct intubation studies with balloons of various portions of the gastrointestinal tract revealed an antispasmodic response with 50 to 100 mg. administered intramuscularly in 23, or 84 per cent, of the subjects. Complete cessation or diminution of motility occurred usually within ten minutes and lasted from fifteen to over ninety minutes (figure). The effect did not appear to be as great as that following medication with atropine, but demerol possessed the same gradient of action as atropine on the stomach, the ileum and the colon in the order named.

TOXICITY

Demerol was found to be safe and with the exception of certain side effects is nontoxic in therapeutic doses. The incidence of side effects for hospitalized and for ambulatory patients is summarized in table 4. These side effects are usually insignificant, are of brief duration and do not as a rule inconvenience the patient to any appreciable degree. Their occurrence is unpredictable, since they may appear after the first dose or only occasionally after several doses. The sex, age and weight of the patient, the diagnosis and the accompanying conditions do not have any relation to the type, frequency and severity of the side effects. After prolonged administration they occur with less frequency, may decrease in their intensity or may subside completely. It is not unusual for a rapid tolerance to the unpleasant reactions to develop and yet the patient may obtain an equal or even better relief of the pain. This tolerance varies for the individual subject. Hospitalized patients may be free of any undesirable reactions within twenty-four to forty-eight hours, no matter how severe they were at the initial dose. On the other hand, mild and usually undisturbing reactions may occur with each dose in ambulatory patients for several weeks or months.

TABLE 4.—*Incidence of Side Effects of Demerol in Hospitalized Patients Treated Parenterally and Orally and in Ambulatory Patients Treated Orally*

Route of Administration	Sex	No. of Patients	Patients with Side Effects		Patients with Significant * Side Effects	
			Number	Percentage	Number	Percentage
Parenteral (hospitalized patients)	Male	464	182	39.2	116	25.0
	Female	310	105	33.9	82	26.4
	Total	774	287	37.1	198	25.5
Oral (hospitalized patients)	Male	330	84	23.4	62	17.3
	Female	311	89	28.6	73	23.4
	Total	670	173	25.8	135	20.1
Oral (ambulatory patients)	Total	138	92	67.6	86	62.5

* Excluding euphoria, perspiration, flushing of the face and dryness of the mouth.

The incidence of the various side effects, significant or otherwise, for each treated group is presented in table 5. The dizziness is mild and is often described as a "feeling of being drunk," "lightheadedness," "floating on air" or "swelling of the head." In ambulatory patients this symptom may be disturbing, particularly

if associated with other reactions. Even then it is well tolerated, particularly if a beneficial relief of pain occurs, so that the patient will continue to take the medication without difficulty. It is unassociated with any cerebellar dysfunction, since nystagmus and ataxia do not occur. As the only manifestation of toxicity it occurred in 6 per cent of the hospitalized patients after parenteral or oral administration and in 15 per cent of the ambulatory patients.

Severe reactions are rare and take the form of extreme weakness; pallor; syncope; profuse, cold and clammy perspiration; marked dizziness; nausea, and vomiting. This syndrome occurred after oral administration in 7 ambulatory and 2 hospitalized patients, the latter being semiambulatory. This type of reaction resembles the vasomotor collapse described by Weiss and co-workers,[24] noted after

TABLE 5.—*Incidence of Side Effects with Demerol*

	Hospitalized Patients				Ambulatory Patients	
	Parenteral Route		Oral Route		Oral Route	
Side Effects	Percentage of All Patients	Percentage of Patients with Side Effects	Percentage of All Patients	Percentage of Patients with Side Effects	Percentage of All Patients	Percentage of Patients with Side Effects
Dizziness	22.1	39.5	18.4	71.1	58.8	87.0
Nausea	8.4	22.6	5.1	19.7	25.7	38.0
Vomiting	3.8	10.4	1.5	5.8	11.8	17.4
Syncope	...	...	0.3	1.2	5.1	7.6
Weakness	0.1	0.3	0.6	2.3	10.3	15.2
Visual disturbance	0.4	1.0	0.7	2.9	3.7	5.4
Headache	0.4	1.0	1.3	5.2	5.9	8.7
Nervousness	0.1	0.3	0.6	2.3	2.2	3.3
Palpitation	...	...	0.1	0.6	...	...
Anxiety	0.1	0.3	0.1	0.6	...	...
Depression	...	...	0.1	0.6	1.5	2.2
Chilly feeling	...	...	0.1	0.6	1.5	2.2
Tremors	0.4	1.0	...	...	5.1	7.6
Disorientation	0.3	0.7	...	...	...	...
Urinary difficulty	0.3	0.7	...	...	...	...
Respiratory depression	0.3	0.7	...	...	...	...
Hangover	...	...	0.3	1.2	1.5	2.2
Perspiration	20.3	54.7	9.6	37.0	20.6	30.4
Dryness of mouth	6.2	16.7	7.2	27.7	18.4	27.2
Euphoria	3.3	22.3	4.0	15.6	9.6	14.1
Warmth	0.8	2.1	0.9	3.5	8.8	13.0
Tinnitus	...	...	0.1	0.6	...	....

administration of nitrites to normal subjects in the upright position. Since demerol possesses vasodilating properties, as demonstrated in experimental animals by studies of blood flow,[25] this response is probably related to an inability to maintain the circulation within compensatory levels when the patient is not recumbent. In this regard, if a patient while ambulatory notes the onset of the reaction, it may be aborted or decreased in severity and duration by the patient's assuming a recumbent position for fifteen to thirty minutes.

In contrast to morphine, urinary retention and respiratory depression occurred rarely with demerol. The latter effect was noted in 2 patients of the 774 receiving the drug parenterally. In both instances the respiratory depression was of short duration and responded readily to the usual stimulants. The first patient had

24. Weiss, S.; Wilkins, R. W., and Haynes, F. W.: Nature of Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Investigation **16**:73, 1937.

25. Unpublished observations.

advanced carcinoma of the esophagus, and the reaction developed after 100 mg. of demerol was given in combination with 0.0004 mg. of scopolamine hydrobromide for preanesthesia. The second patient was markedly debilitated with generalized arteriosclerosis and presented the respiratory depression after a dose of 100 mg. of the drug, even though for the previous month repeated injections of the same dose had not produced any untoward effects. In several cases in which morphine had previously produced respiratory depression demerol was easily substituted without causing this reaction.

Prolonged use of demerol did not result in any alteration of the hemopoietic system or impairment of renal function. In a few ambulatory patients anorexia was a prominent complaint at the onset of therapy, but this soon subsided, with restoration of normal appetite. On the other hand, many patients noted an improvement of their appetite. Constipation, which occurs in practically every patient treated with opiates, never resulted from medication with demerol.

It is of particular interest to note the occurrence of euphoria. Although it is listed as a side effect, the state of well-being may be considered a desired therapeutic effect. It is not noted in more than 8 to 10 per cent, which is considerably lower than the 90 per cent reported by Barlow [7] for normal subjects. The presence of pain, other accompanying side effects and the hospital atmosphere may explain the difference in incidence.

Finally, the drug may be given without fear to patients receiving sulfonamide compounds, since they did not appear to affect the potency or the safety of demerol.

PHARMACOLOGIC STUDIES IN MAN

In addition to the gastrointestinal intubation studies mentioned previously, extensive pharmacologic studies in man were undertaken to evaluate the drug's safety and its other actions besides analgesia. The electrocardiogram and the basal metabolic rate remain unaltered. The blood pressure and the ventricular rate are unaffected in therapeutic doses except in those patients presenting syncope, in which case the blood pressure falls moderately and the rate decreases. Unlike morphine demerol does not change the size of the pupil, and the pupillary reflexes can still be elicited. It is of interest to note that the corneal reflex and the sensitivity of the cornea are abolished in approximately 80 per cent of subjects. Drowsiness and sleep occur with the larger doses usually after parenteral administration, are of short duration and are not followed by depression or confusion.

COMMENT

For centuries opiates have been the most effective drugs for the relief of pain. Although they possess many undesirable side effects and disadvantages, their potency is such that their use became mandatory when severe pain was present. It is therefore unfortunate that other analgesic drugs, notably the coal tar derivatives, were ineffective for this type of pain. This is of particular importance in the treatment of chronic conditions, in which the indiscriminate use of a potent narcotic usually leads to development of physical dependence on the drug. Demerol is the first drug which appears to be of value in those patients who ordinarily would have required opiates for relief. With rare exceptions the pain and restlessness of patients after operation are more than satisfactorily controlled. Visceral pain, such as peritoneal and pleuritic irritation, as well as colicky pains of all types, is immediately relieved, with a minimum of undesirable side reactions. Conditions associated with chronic pain are also greatly relieved and the patients made comfortable with an appropriate dose of demerol, or once any side effects, if initially present,

subside. It is essential to reemphasize the fact that demerol is merely a symptomatic measure and not a cure. In patients with chronic pain, a single dose may result in alleviation of the pain for only two to four hours, at which time, if no further medication is given, the pain returns to its original intensity. This may be overcome by administering the drug several times at definite intervals of three to four hours at which time a maximum and prolonged analgesic effect is usually achieved.

The sedative effect is definite but not marked. Restlessness is immediately relieved, and in the majority of instances after parenteral administration of large doses sleep may be induced. This is of short duration, usually less than the period of analgesia, but when the drug is given at night, the effect may merge into natural and restful sleep which lasts for several hours. The orally administered dose may not be effective for this purpose, and if a soporific effect is desired in addition to analgesia other somnafacients may be necessary. In contrast to morphine and codeine, excitation is rarely if ever observed with demerol.

In both the hospitalized and the ambulatory patients, who took the drug for many weeks and months, it was impossible to establish with any certainty that tolerance to the general analgesia occurs. A few patients required an increased dose to obtain relief of pain. However, the patients' conditions may have changed and the pain increased in severity. In fact, in several of these patients it was possible to return to a smaller dose or to the original dose to achieve the same effect as that gained at the onset of therapy.

Although tolerance may develop for the effect by which the threshold for cutaneous pain is raised, as demonstrated by Andrews,[26] and for the side reactions, we feel that the likelihood of its occurrence for general analgesia is remote.

The question of addiction liability must be considered carefully in view of the drug's resemblance to morphine particularly in producing euphoria and in its ability to satisfy partially the "need" for opiates in patients already addicted. By the term addiction is meant the development of physical dependence on a drug, so that on its withdrawal symptoms and signs indicative of its need become manifest. On the other hand, habituation represents the psychic craving for a drug to maintain a state of well-being or to achieve a desired effect, such as euphoria, analgesia or sedation. In the latter case withdrawal symptoms do not result when administration of the drug is discontinued.

European observers [27] and recently Himmelsbach [28] have reported on the liability of addiction to demerol. There is no question that the administration of demerol without restriction of dose to addicts or postaddicts will cause physical dependence on and abuse of the drug. In my own patients receiving the drug in controlled doses for several weeks or months, there has been no instance of primary addiction. However, in view of the present limited experience with the drug, the possibility of the occurrence of addiction after extended administration in patients with chronic illness has not been excluded. The question requires further study and can be answered only by trial on patients who have not previously received opiates. At the present time it can be stated that demerol may result in habituation. In a few instances, because of the analgesic and sedative effect or the occurrence of euphoria,

26. Andrews, H. L.: The Development of Tolerance to Demerol, J. Pharmacol. & Exper. Therap. **75**:338, 1942.

27. Kucher, I.: Zwei Fälle von Dolantinsucht, Klin. Wchnschr. **19**:688 (July 6) 1942. von Brücke, S.: Ueber Dolantinabusus und einen Fall von Dolantindelir, Wien. klin. Wchnschr. **53**:854 (Oct. 18) 1940.

28. Himmelsbach, C. K.: The Addiction Liability of Demerol-(1-Methyl-4-Phenyl-Piperidine-4-Carbonic Acid Ethyl Ester), J. Pharmacol. & Exper. Therap. **75**:64, 1942.

desire for the drug was expressed. However, none of these patients experienced any untoward reaction on withdrawal of the drug.

For hospitalized patients the average therapeutic dose of demerol is 50 to 100 mg. administered orally or parenterally. If this dose is unsatisfactory, it may be increased by increments of 25 mg. until a desired effect is achieved or 200 mg. is being administered. It is unlikely that higher doses would be necessary, since it is unusual for a patient not to respond to a dose under 150 mg. However, if analgesia is not obtained with a dose as high as 200 mg., the probability of the patient's responding to a higher dose is remote. Furthermore, it has been my experience that an equivalent dose of morphine is also unlikely to produce a greater effect in such a case. With severe and acute pain a dose of 100 mg. may be repeated in one or two hours if necessary. If side effects occur with the average dose and continue to occur with the same severity on subsequent doses, they may be prevented or decreased by giving a smaller dose of 25 to 50 mg. until a tolerance develops for the undesirable reactions. It is then possible to return to the larger dose for the analgesic effect.

The initial dose for the ambulatory patient should be 50 mg. at intervals of four hours. The patient should be cautioned as to the possibility of the occurrence of dizziness and weakness and advised to assume a supine position if these are severe. These symptoms usually subside quickly and gradually become less disturbing if the medication is continued. The dose may be increased to 75 or 100 mg. if necessary.

Demerol offers several advantages. Besides being synthetic and a potent analgesic, it is relatively free of any serious toxic manifestations. Its use for conditions previously responding only to morphine allows the latter drug to be reserved for use in refractory cases. Respiratory depression and urinary difficulty are rare following its use. The absence of disturbance of pupillary reflexes makes the drug particularly useful for head injuries and other intracranial conditions. In contrast to the opiates, it may be used without fear in patients with severe anemia, disease of the liver or kidneys or bronchial asthma. Its antispasmodic action makes the drug ideal for the treatment of severe colicky pain. Finally, its general analgesic effects can be elicited for weeks or months after intensive therapy without any appreciable tolerance developing. The high incidence of side effects in ambulatory patients and the rapid dissipation of the drug from the body are two minor disadvantages. The former is only of temporary importance, since the side effects subside with prolonged use, and the short duration of analgesia may be overcome by administering the drug more often.

CONCLUSION

Demerol, a new synthetic analgesic, was studied in 1,119 hospitalized patients and found to be potent, effective and safe for the relief of pain due to a variety of medical and surgical conditions. It could be used in patients who ordinarily would have required opiates for relief. Hospitalized patients are relatively free of serious side effects, but because of the high incidence of dizziness and the possibility of syncope the drug should be used with caution on ambulatory patients.

This investigation was carried out under the direction of Prof. Arthur C. DeGraff. Miss Aniele C. Evaskitis, research nurse of the Department of Therapeutics, New York University College of Medicine, assisted me in the pharmacologic studies and in obtaining data on the patients receiving demerol.

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EFFECTIVE RENAL BLOOD FLOW, GLOMERULAR FILTRATION RATE AND TUBULAR EXCRETORY MASS IN ARTERIAL HYPERTENSION

II. EFFECT OF SUPRADIAPHRAGMATIC SPLANCHNICECTOMY WITH LOWER DORSAL SYMPATHETIC GANGLIONECTOMY

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In a previous paper [1] we reported the results of the determination of effective renal blood flow, glomerular filtration rate and tubular excretory mass by the diodrast and inulin clearance methods in 20 patients with arterial hypertension. It was concluded that arterial hypertension is associated with renal ischemia and that the reduction of blood supply to the kidney shows a definite correlation with the severity of the disease, as indicated by the changes, in the eyegrounds, the degree of thickening of the systemic arterioles, the renal function and the elevation of systolic and diastolic blood pressures. While this previous paper was in press, the results of similar studies were published by other investigators [2] who also concluded that the rate of renal blood flow is decreased in most cases of hypertension.

The purpose of this paper is to report the results of the determination of effective renal blood flow, glomerular filtration rate and tubular excretory mass after supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy in patients who had been studied preoperatively. Peet, Woods and Braden [3] reported the clinical results of this operation in the treatment of 350 patients with arterial hypertension and found that in 51.4 per cent the blood pressure was significantly reduced.

Several hypotheses have been advanced to explain why different operations on the sympathetic nervous system frequently cause a drop in blood pressure.

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1. Foà, P. P.; Woods, W. W.; Peet, M. M., and Foà, N. L.: Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass in Arterial Hypertension, Arch. Int. Med. **69**:822 (May) 1942; abstracted, Am. J. Path. **17**:446 (May) 1941.

2. Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Hypertension as Determined in Patients with Variable, with Early and with Long-Standing Hypertension, J. A. M. A. **117**:92 (July 12) 1941. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subjects with Essential Hypertension, J. Clin. Investigation **20**:637 (Nov.) 1941. Chasis, H., and Redish, J.: Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension, ibid. **20**:655 (Nov.) 1941.

3. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension, J. A. M. A. **115**:1875 (Nov. 30) 1940.

According to one theory, the denervation of the adrenal glands, which is more or less extensively accomplished by most of the operations recommended, decreases the hyperepinephrinemia to which hypertension is attributed. A second hypothesis is that the operation dilates the vessels controlled by the resected nerves, thus creating a large vascular bed with decreased resistance in the splanchnic area. As a working hypothesis, Peet [4] suggested that his type of splanchnicectomy dilates the renal arterioles and increases the blood flow through the kidneys in patients with arterial hypertension, thus attacking directly what might be considered the primary cause of the disease. Finally, we wish to present in this paper the hypothesis that improvement in blood pressure following splanchnicectomy is due to an increased pulse pressure in the renal arterioles.

It has been shown that section of different parts of the sympathetic nervous system cannot prevent or cure hypertension produced experimentally by clamping the renal arteries.[5] This fact has often been used as an argument against the surgical treatment of hypertension. It should be emphasized, however, that whereas the interruption of nervous pathways cannot modify renal circulation obstructed by an irremovable metal clamp, it could remove an obstruction due to a reversible spastic contraction of the renal arterioles. Evidence that in certain circumstances renal circulation is controlled by the nervous system has been presented.[6] As a matter of fact, renal denervation has proved effective in preventing or curing other forms of experimental hypertension, such as the one due to oxalate nephritis,[7] or the one due to injection of kieselguhr (purified siliceous earth) into the renal artery.[8] According to Grimson,[9] complete sympathectomy prevents and cures hypertension due to resection of the carotid and aortic depressor nerves.

METHODS AND CRITERIA

Diodrast and inulin clearances have been determined, with the same technic and precautions as in the preoperative studies.[1] From these determinations effective renal blood flow, glomerular filtration rate and tubular excretory mass have been computed. The principles of these methods have been extensively discussed by Smith and his associates.[10] They are

4. Peet, M. M.: Splanchnic Section for Hypertension: A Preliminary Report, Univ. Hosp. Bull., Ann Arbor **1**:17 (June) 1935.

5. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826 (Nov.) 1937. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, Am. Heart J. **14**:405 (Oct.) 1937. Goldblatt, H., and Wartman, W. B.: Studies on Experimental Hypertension: VI. The Effect of Section of Anterior Spinal Nerve Roots on Experimental Hypertension Due to Renal Ischemia, J. Exper. Med. **66**:527 (Nov.) 1937. Goldblatt, H.; Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension: II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, ibid. **65**:233 (Feb.) 1937. Glenn, F., and Lasher, E. P.: The Effect of Destruction of the Spinal Cord on the Artificial Production of Hypertension in Dogs, Am. J. Physiol. **124**:106 (Oct.) 1938.

6. Herrick, J. F.; Essex, H. E., and Baldes, E. J.: Observations on the Flow of Blood of the Kidney, Am. J. Physiol. **99**:696 (Feb.) 1932. Schneider, M., and Wildbolz, E.: Dekapsulation und Enervation der Niere und Nierendurchblutung, Ztschr. f. urol. Chir. **43**:1, 1937. Hermann, M., and Jourdan, F.: Vérification par la méthode des dégénérescences de la systématisation ganglionnaire des voies vasoconstrictives du rein, Compt. rend. Soc. de biol. **124**:1108, 1937.

7. Arnott, W. M., and Kellar, R. J.: The Effect of Renal Denervation on the Blood Pressure in Experimental Renal Hypertension, J. Path. & Bact. **42**:141 (Jan.) 1936.

8. Maegraith, B. G., and McLean, F. J.: Experimental Renal Hypertension in Rabbits: Effect of Section of Renal Nerves, J. Physiol. **92**:44 P (Feb.) 1938.

9. Grimson, K. S.: The Sympathetic Nervous System in Neurogenic and Renal Hypertension, Arch. Surg. **43**:284 (Aug.) 1941.

10. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263 (May) 1938.

based on the facts that at low plasma concentration diodrast is practically completely cleared in one passage of the plasma through the kidneys and that therefore diodrast clearance measures the flow of plasma through the active renal tissue. When the concentration of diodrast in the plasma is increased enough to saturate the kidneys, the excretion of this substance reaches a maximum. This is proportional to the amount of excretory tissue and, expressed in milligrams of iodine excreted per minute, is used as a measure of the tubular excretory mass (Tm_D). Inulin is excreted only by glomerular filtration and is not reabsorbed by the tubules. Its clearance is therefore a measure of the filtration rate.

The eyegrounds of every patient have been reexamined and regrouped according to the Keith-Wagener classification and by objective findings, such as hemorrhages, exudates and papilledema.

Blood pressure readings were always taken by the same observer and under uniform conditions. Briefly, the patient was reclining; the blood pressure was taken from the right arm; the diastolic pressure was read when the sound first became dull, since in patients with hypertension it is frequently impossible to determine sharply the disappearance of all sounds. The recommendations of the American Heart Association[11] were followed in all other respects.

The term "blood pressure on admission" (see tables) is used to denote the blood pressure measured when the patient was admitted to the hospital before the operation and also when he was readmitted for the postoperative examination after five or more months. The term "blood pressure during test" is used to denote the average of all the blood pressure readings obtained during each determination of inulin and diodrast clearances. Blood pressure readings were taken approximately every five minutes for about three hours.

In the comment which follows on the effect of splanchnicectomy on renal circulation, an increase or decrease of 20 or more mm. of mercury systolic and 10 or more mm. of mercury diastolic in "blood pressure during test" was considered a significant change. No change of less than 15 mm. in mean blood pressure or of less than 10 mm. in pulse pressure was considered significant. We feel that these differences are great enough to rule out the possibility of an error of determination. In evaluating clinical results, however, for which daily and weekly fluctuations of blood pressure must be taken into account, the criteria of Peet, Woods and Braden[8] were used and a change of 40 systolic and 15 diastolic or more was considered significant.

RESULTS

Of the 20 patients reported on in our previous paper,[1] 2 (S. M. and D. M.) died before any postoperative examination could be made, and 3 (E. J., N. E. and T. S.) did not return for reexamination. For 15 patients the tests were repeated in from two weeks to twelve months after the operation. Two patients (B. E. and N. N.) who were not included in the first series are included in the group used for this paper.

Table 1 contains the average results of the tests, which were made shortly after the patients, 15 in number, had recovered from the operation, and when they were about to be discharged. Patient L. C., who returned for her first postoperative examination two months after the operation, is included in table 1.

Table 2 contains the average results obtained for those patients, 15 in number, who were studied in from five to twelve months after the operation. Thirteen of our patients had two postoperative examinations and are included in tables 1 and 2.[12]

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11. Standardization of Blood Pressure Readings, Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, Am. Heart J. 18:95 (July) 1938.

12. The reader will notice that the average preoperative values are not the same in table 1 as in table 2 and that they also differ from the average preoperative values given in the preceding paper. This is due to the fact that in each table preoperative averages were computed only on those patients who were examined at the postoperative time under consideration and that not all the patients who were reexamined two weeks after operation had a later check-up, or vice versa. Moreover, not all the patients who were studied preoperatively had further studies, and 2 new patients not reported in our preceding paper are included in these tables.

TABLE 1.—*Averages of Data Obtained on Reexamination Approximately Two Weeks After Operation*

	Group 1 Markedly Reduced Renal Blood Flow		Group 2 Moderately Reduced Renal Blood Flow		Total Average	
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
Blood pressure, mm. Hg						
Systolic and diastolic	203/123	190/124	176/111	165/111	186/118	173/115
Mean pressure	168	157	144	138	152	144
Pulse pressure	70	66	65	54	66	58
Effective renal blood flow, cc. per min.	346.9	418.4	781.0	728.6	647.41	632.41
Filtration rate (C_{In}), cc. plasma per min.	58.1	69.3	120.5	112.46	101.31	99.2
Filtration fraction (FF), percentage	26.68	22.58	26.18	26.06	26.34	24.99
Tubular excretory mass (Tmp) in mg. iodine per min.	.....	.....	35.73	41.0	35.73	41.0
Ratio of diodrast clearance to excretory mass (C_D/Tmp)‡	.....	.....	13.70	10.91	13.70	10.91
Ratio of inulin clearance to excretory mass (C_{In}/Tmp)	.....	.....	3.82	2.73	3.82	2.73
Arteriolar ratio, wall/lumen	1.0405		0.9367		0.9783	
Eyegrounds						
Keith-Wagener classification						
Normal	0		3		3	
Group I	0		0		0	
Group II	0		1		1	
Group III	2		5		7	
Group IV	4		0		4	
Objective findings						
Normal	0		3		3	
Sclerosis only	0		1		1	
Spasm only	2		1		3	
Spasm and sclerosis	0		3		3	
Retinitis	4		1		5	

‡ C_D, Effective renal plasma flow (diodrast clearance).

TABLE 2.—*Averages of Data Obtained on Reexamination Five to Twelve Months After Operation*

	Group 1 Markedly Reduced Renal Blood Flow		Group 2 Moderately Reduced Renal Blood Flow		Total Average	
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
Blood pressure, mm. Hg						
On admission						
Systolic and diastolic	229/131	172/111	212/137	159/103	217/135	163/106
Mean pressure	180	142	175	131	176	135
Pulse pressure	98	61	75	56	82	57
During test						
Systolic and diastolic	197/128	169/110	176/118	159/102	183/117	160/104
Mean pressure	163	140	145	131	150	132
Pulse pressure	68	59	63	57	66	56
Effective renal blood flow, cc. per min.	427.5	510.4	764.6	682.4	680.9	629.45
Filtration rate (C_{In}), cc. plasma per min.	75.5	99.4	115.16	143.65	102.94	130.05
Filtration fraction (FF), percentage	29.81	33.09	25.15	33.00	27.37	33.03
Tubular excretory mass (Tmp) in mg. iodine per min.	.....	.....	35.96	35.05	35.96	35.05
Ratio of diodrast clearance to excretory mass (C_D/Tmp)	.....	.....	11.63	12.05	11.63	12.05
Ratio of inulin clearance to excretory mass (C_{In}/Tmp)	.....	.....	3.95	5.32	3.95	5.32
Arteriolar ratio, wall/lumen	1.1124		0.9323		1.0095	
Eyegrounds						
Keith-Wagener classification						
Normal	0	0	3	2	3	2
Group I	0	0	0	0	0	0
Group II	0	2	1	4	1	6
Group III	3	4	5	3	8	7
Group IV	3	0	0	0	3	0
Objective findings						
Normal	0	0	3	2	3	2
Sclerosis only	0	2	1	3	1	5
Spasm only	2	2	0	3	2	5
Spasm and sclerosis	0	0	4	0	4	0
Retinitis	4	2	1	1	5	3

Patient	Age	Sex	Time	Blood Pressure on Admission, Mm. Hg: Blood Pressure	Mean	Pulse	Blood Pressure During Test, Mm. Hg: Blood Pressure	Mean	Pulse	Effective Renal Blood Flow, Cc. per Min.	Filtration Rate, (CIn) Cc. Plasma per Min.	Filtration Fraction, per Cent	Tubular Excretory Mass (Tm), Mg. Iodine per Min.	Ratio of Diodrast Clearance to Excretory Mass (Cn/Tmn)	Ratio of Inulin Clearance to Excretory Mass (Cin/Tmn)	Arterioles, Wall/Lumen	Eyegrounds: K-W *	Eyegrounds: Changes †
N. N.	23	M	Preop.	260/160	210	160	199/141	170	58	111.1	18.6	25.2	42.2	26.3	4.41	1.168	III	H; Ex; Sp; Sc
			Postop. 2 wk.	.....	...	...	143/117	130	26	56.61	5.67	12.92	....	....	....	.....	III	H; Ex; Sp; Sc
A. O.	34	F	Preop.	220/140	180	80	210/126	168	84	201.8	....	....	....	....	....	1.0494	IV	H; Ex; Ed
			Postop. 2 wk.	.....	...	..	216/121	168	85	364.8	....	....	....	....	....	.....	...	.....
			Postop. 6 mo.	214/142	178	72	214/142	181	72	346.1	....	....	....	....	....	.....	III	Ex; Sp; Sc
C. D.	42	F	Preop.	250/120	185	130	219/127	173	92	250.9	45.8	27.83	....	....	....	1.755	IV	H; Ex; Ed
			Postop. 2 wk.	.....	...	...	228/125	176	103	551.2	78.2	18.9	....	....	....	.....	...	.....
			Postop. 7 mo.	199/118	158	81	206/119	158	87	512.2	59.6	17.44	....	....	....	.....	III	H; Ex; Sp
W. J.	34	M	Preop.	200/130	165	70	171/119	145	52	433.6	87.9	37.7	....	....	....	1.599	III	H; Ex; Sp
			Postop. 6½ mo.	125/ 93	109	32	124/ 90	107	34	439.1	158.3	55.16	....	....	....	.....	II	Sc
F. E.	46	F	Preop.	220/130	175	90	212/131	171	81	496.7	85.0	27.03	30.6	10.98	2.78	0.0012	III	Sp
			Postop. 2 wk.	.....	...	..	207/126	161	81	412.4	86.75	31.46	....	....	....	.....	...	.....
			Postop. 12 mo.	208/129	168	80	205/131	168	74	474.0	99.6	36.29	17.7	26.76	5.63	.....	III	Sp
D. C.	51	M	Preop.	190/120	155	70	118/ 87	102	31	506.7	....	....	....	....	....	0.9063	IV	Sp; Ed
			Postop. 2 wk.	.....	...	..	187/132	161	55	647.3	....	....	....	....	....	.....	...	.....
			Postop. 10 mo.	185/129	157	56	172/122	147	50	624.1	....	....	....	....	....	.....	III	Sp
V. P.	37	M	Preop.	245/145	195	100	184/133	159	51	528.8	83.1	26.68	....	....	....	0.7645	III	Sp
			Postop. 2 wk.	.....	...	...	180/128	154	52	653.2	106.4	26.04	....	....	....	.....	...	.....
			Postop. 6 mo.	156/104	130	52	141/100	120	41	616.3	80.0	23.49	....	....	....	.....	II	Sc
S. M.	40	F	Preop.	185/140	162	45	157/105	131	52	643.0	61.4	15.44	....	....	....	0.7499	III	Sp; Sc
			Postop. 5 mo.	126/ 89	107	37	124/ 86	104	38	353.0	79.45	34.5	....	....	....	.....	II	Sc
E. J.	36	M	Preop.	240/170	205	70	187/127	155	57	649.8	73.2	19.4	....	....	....	0.8191	III	H; Ex; Sp
			Postop. 2 wk.	.....	...	..	210/157	183	53	486.0	113.9	38.75	....	....	....	.....	...	.....
			Postop. 6 mo.	234/149	191	85	212/142	177	70	565.8	89.4	27.39	....	....	....	.....	III	Sp
S. B.	39	F	Preop.	225/130	177	95	208/123	163	80	609.5	119.8	28.43	42.84	9.75	2.80	0.9011	III	Sp; Sc
			Postop. 2 wk.	.....	...	..	148/ 96	122	52	527.0	91.3	26.04	33.48	10.62	2.65	.....	...	.....
			Postop. 7 mo.	142/ 90	116	52	142/ 87	114	55	741.0	215.0	44.6	26.2	18.4	8.22	.....	II	Sc
W. C.	52	F	Preop.	230/130	180	100	188/102	145	86	681.8	120.6	30.48	28.2	13.9	4.28	1.367	III	Sp
			Postop. 2 wk.	.....	...	...	182/112	147	70	634.7	102.8	27.71	30.4	12.3	3.38	.....	...	.....
			Postop. 7 mo.	160/ 97	128	63	156/ 99	127	57	599.1	103.8	27.92	24.6	14.11	4.22	.....	III	Sp
B. E.	16	M	Preop.	200/150	175	50	188/137	162	51	691.75	176.3	42.76	50.11	8.14	3.45	1.012	Normal	
			Postop. 3 wk.	.....	...	..	169/139	154	30	594.6	95.8	26.7	35.23	10.45	2.72	.....	...	.....
			Postop. 6½ mo.	166/123	144	43	168/123	145	45	809.1	129.5	28.46	33.05	14.95	3.92	.....	? III	? Sp
G. S.	44	M	Preop.	200/120	160	80	158/ 92	125	64	788.7	109.5	24.74	34.59	13.44	3.18	0.5709	III	Sp
			Postop. 2 wk.	.....	...	..	146/ 93	119	53	904.4	104.5	18.96	47.75	11.71	2.19	.....	...	.....
O. C.	28	M	Preop.	210/150	180	60	148/106	127	42	804.0	125.8	25.93	25.46	18.6	4.95	1.051	Normal	
			Postop. 1½ wk.	.....	...	..	147/102	124	45	645.8	88.0	25.0	50.4	7.9	1.75	.....	...	.....
			Postop. 7 mo.	120/ 90	105	30	122/ 87	104	35	662.3	174.3	40.62	34.81	12.45	5.0	.....	Normal	
A. A.	42	F	Preop.	215/135	175	80	198/126	162	72	807.9	143.9	26.16	....	....	....	1.151	II	Sc
			Postop. 2 wk.	.....	...	..	210/126	168	84	839.08	156.0	25.95	....	....	....	.....	...	.....
			Postop. 8½ mo.	167/110	138	57	170/110	140	60	686.1	121.0	25.68	....	....	....	.....	III	Sp; Sc
H. M.	39	F	Preop.	210/120	165	90	171/108	139	63	846.0	74.5	15.49	....	....	....	0.9914	III	Sp; Sc
			Postop. 2 wk.	.....	...	..	175/109	142	66	899.4	82.0	15.94	....	....	....	.....	...	.....
			Postop. 7 mo.	178/114	146	64	175/108	142	67	548.66	84.4	26.08	....	....	....	.....	II	Sc
L. C.	26	F	Preop.	190/110	150	80	162/ 81	121	81	1688.5	140.95	22.27	33.17	19.4	4.25	0.567	Normal	
			Postop. 2 mo.	.....	...	..	120/ 69	94	51	1017.0	177.9	29.52	48.69	12.5	3.65	.....	...	.....
			Postop. 8 mo.	135/ 67	101	68	130/ 72	98	58	1067.0	296.3	41.74	56.6	12.38	5.24	.....	Normal	

* K-W, the Keith-Wagener classification of hypertensive patients based on the condition of the ocular fundus.
† H, hemorrhages; Ex, exudates; Ed, papilledema; Sp, angiospasm; Sc, sclerosis.

Tables 3 and 4 contain data obtained on individual patients.

The data show that, on the average, two weeks after the operation there was no significant change in blood pressure or in renal circulation, although there were minor temporary changes in individual patients. Five to twelve months after the operation systolic, diastolic and pulse pressures were reduced in a good percentage of cases, but these changes were not accompanied by significant changes in the renal blood flow. As will be discussed later, we feel that this is significant. It is also apparent from the tables that frequently the final results of the operation appear only after several months and that no definite conclusions can be drawn when there is a short period of postoperative observation.

Approximately two weeks after splanchnicectomy (table 1) the effective renal blood flow averaged 647.41 cc. per minute, as compared with 632.41 cc. per minute in the same patients before the operation, a change which may be considered insignificant. The filtration rate (C_{In}) and filtration fraction (FF) did not change significantly either, averaging respectively 101.31 and 26.34 before the operation

TABLE 4.—*Relation Between Drop in Blood Pressure and Changes in Renal Blood Flow Five to Twelve Months After Operation*

Patient	Blood Pressure on Admission, Mm. Hg		Postoperative Renal Blood Flow as Compared to Preoperative
	Preoperative	Postoperative	
Group 1			
A. O.	220/140	214/143	Increased
C. D.	250/120	199/118	Increased
W. J.	200/130	125/ 90	Unchanged
F. E.	220/130	208/128	Unchanged
D. O.	190/120	185/129	Doubtfully increased
V. P.	245/145	156/104	Unchanged
Group 2			
S. M.	185/140	126/ 80	Decreased
E. J.	240/170	234/140	Unchanged
S. B.	225/130	142/ 90	Unchanged
W. C.	230/130	160/ 97	Unchanged
B. E.	200/150	166/128	Doubtfully increased
O. C.	210/150	120/ 90	Unchanged
A. A.	215/135	167/110	Unchanged
H. M.	210/120	178/114	Doubtfully decreased
L. C.	190/110	135/ 67	Unchanged

and 99.2 and 24.99 two weeks after the operation. The tubular excretory mass (Tm_D) increased from 35.73 to 41.0, and accordingly the blood flow and filtration rate per unit of tubular excretory mass (C_D/Tm_D and C_{In}/Tm_D) decreased from 13.7 to 10.91 and from 3.82 to 2.73 respectively. The average systolic and diastolic "blood pressures during the test" were 186 and 118 before the operation and 173 and 115 two weeks after. The average mean blood pressure was 152 before and 144 after, and the average pulse pressure dropped from 68 to 58.

Five to twelve months after splanchnicectomy (table 2) the effective renal blood flow averaged 629.45 cc. per minute, as compared with 660.9 cc. per minute in the same patients before the operation, which is not a significant change. The average filtration rate rose from 102.94 cc. per minute to 130.05 cc. per minute, and accordingly the average filtration fraction increased from 27.37 to 33.03 per cent. The tubular excretory mass remained relatively unchanged, averaging 35.96 before the operation and 35.05 after it. The blood flow per unit of tubular excretory mass (C_D/Tm_D) did not change significantly, being 11.63 before the operation and 12.05 after it. The filtration rate per unit of tubular excretory mass (C_{In}/Tm_D) rose from 3.95 to 5.32.

The systolic and diastolic pressures "during the test" averaged 183 and 117 before the operation and dropped to an average of 160 and 104 five to twelve months after the operation. The average mean blood pressure "during the test" dropped from 150 to 132, and the pulse pressure, from 66 to 56. The average "blood pressure on admission," systolic and diastolic, dropped from 217 and 135 to 163 and 106, and the average pulse pressure, from 82 to 57.

The foregoing are the average data. If the results obtained for the individual patients are now examined (table 3), it is again observed that no permanent significant changes in blood pressure or renal blood flow were obtained within two weeks after the operation, but that within from five to twelve months after the operation in a good number of cases the blood pressure was reduced without any significant change in renal blood flow.

"Blood Pressure on Admission."—According to the standards arbitrarily established for evaluating clinical results, 8 of the 15 patients who were examined five or more months after the operation had a significant drop in "blood pressure on admission" (i. e. more than 40 systolic and 15 diastolic) and 7 had no improvement. Of these 7, however, E. J. had a drop of 21 mm. in diastolic pressure, B. E. a drop of 34 systolic and 27 diastolic and H. M. a drop of 32 systolic and 6 diastolic. The 8 patients whose blood pressures were improved had no change in renal blood flow. It is interesting to note that neither of the 2 patients whose renal blood flow increased had a reduction in blood pressure; in fact, 1 had an increase of 13 in mean pressure.

"Blood Pressure During Test."—Two weeks after the operation the "blood pressure during test" was reduced more than 20 mm. systolic and 10 mm. diastolic in 3 patients out of 15 examined at this time. Five to twelve months after the operation, however, the number of patients in whom the "blood pressure during test" was reduced 20 systolic and 10 diastolic had increased to 8 out of 15. The pulse pressure was reduced by 10 or more in 8 out of 15.

Effective Renal Blood Flow.—Two weeks after the operation, the effective renal blood flow was unchanged in 7 patients and increased in 2 patients. However, it remained extremely low in both of them. A doubtfully significant change in renal blood flow was noted in 8 patients. These results were, however, temporary. Five to twelve months after the operation (table 4) the renal blood flow showed no significant change, returning to approximately the preoperative values in 13 of 15 patients.

Filtration Fraction.—Two weeks after the operation, the filtration fraction was reduced in 6 patients, unchanged in 4 patients and increased in 3 patients. Five to twelve months after the operation the picture was again changed. The filtration fraction was increased in 8 patients, of whom 4 had had a decrease or no change in this fraction two weeks after the operation. In only 3 patients was a reduction in filtration fraction maintained for from five to twelve months after the operation. In 1 case the filtration fraction, which was found unchanged two weeks after the operation, was decreased ten months later. It may be said, therefore, that the changes in filtration fraction after operation are not uniform.

Tubular Excretory Mass.—The tubular excretory mass, two weeks after the operation, was increased in 3 patients, unchanged in 1 patient and decreased in 2 patients. Five to twelve months after the operation, the results were approximately the same.

In our paper on preoperative studies [1] the patients were divided into two groups according to their effective renal blood flow, and it was pointed out that patients in group 1, with a lower renal blood flow, were more severely ill than patients in

group 2, who had a relatively higher renal blood flow. The average wall/lumen ratio of the systemic arterioles was 1.241 in group 1 and 1.009 in group 2, showing a greater organic thickening of the arteriolar wall in the patients of group 1 than in those of group 2. This grouping has proved to be of prognostic value. Seven of the 12 patients in group 1 had malignant hypertension, and 4 died (N. N., S. M., A. O. and D. M.). A fifth (E. J.) left the hospital in extremely poor condition, and it has been impossible to communicate with him. Only 2 (W. J. and V. P.) had a persistent drop in blood pressure of 40 systolic and 15 diastolic. One did not return for reexamination, and the other 3 had a drop in blood pressure which is probably significant although not sufficient to meet our arbitrary standards.

COMMENT

The effect of sympathectomy on the renal circulation of patients with essential hypertension has been reported recently by other authors.[13] They have concluded that sympathectomy does not modify the renal circulation. My associates and I must disagree with this conclusion for two reasons: First, the postoperative observation period was too short. It has been pointed out in a preceding paragraph that not infrequently the immediate effects of operation differ considerably from those observed several months later. Second, in the cases presented by Corcoran and Page [13b] and by Selzer and Friedman [13c] the blood pressure was not significantly reduced during the short period of postoperative observation. We feel that a drop in blood pressure is all important in reaching a conclusion as to the effects of the operation on the renal circulatory system. If no reduction of the blood pressure is obtained, possibly because the organic changes in the systemic arterioles are too far advanced to be reversible, one does not expect any change in the arterioles of the kidney by interruption of the vasoconstrictor fibers.

Our results indicate that bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathectomy does not significantly change the rate of effective renal blood flow or the tubular excretory mass of patients with arterial hypertension, irrespective of the effect on the blood pressure. The question arises whether "renal ischemia" can be considered the primary cause of hypertension in man. It may be that the ischemia of the kidneys is simply another aspect of the generalized arteriolar disease. Ever since Goldblatt first produced experimental hypertension by reducing the lumens of the renal arteries, it has been customary to refer to this type of hypertension as "hypertension due to renal ischemia." If the generally accepted meaning of the word ischemia, which is "reduced blood supply," is used, it becomes doubtful whether it indicates the condition in the kidneys of Goldblatt animals. In these animals the renal blood flow is not necessarily reduced once hypertension becomes established, because the increase in aortic pressure may compensate for the narrowing of the renal artery. As a matter of fact, Mann, Herrick, Essex and Baldes [14] have shown that the lumen of an artery must be greatly reduced before a significant reduction in blood flow can be obtained. Schroeder and Steele [15] measured the renal blood flow with a

13. (*a*) Alving, A. S.; Adams, W.; Grimson, K. S.; Scott, C., and Sandiford, I.: Effect of Bilateral Paravertebral Sympathectomy on the Cardiorenal System in Essential Hypertension, Proc. Inst. Med. Chicago **13**:306 (Feb. 15) 1941. (*b*) Corcoran, A. C., and Page, I. H.: Renal Blood Flow and Sympathectomy in Hypertension, Arch. Surg. **42**:1072 (June) 1941. (*c*) Selzer, A., and Friedman, M.: Effect of Bilateral Splanchnicectomy upon Renal Blood Flow in Hypertension, Proc. Soc. Exper. Biol. & Med. **48**:429 (Nov.) 1941.

14. Mann, F. C.; Herrick, J. F.; Essex, H. E., and Baldes, E. J.: The Effect on the Blood Flow of Decreasing the Lumen of a Blood Vessel, Surgery **4**:249 (Aug.) 1938.

15. Schroeder, H. A., and Steele, J. M.: The Behavior of Renal Blood Flow After Partial Constriction of the Renal Artery, J. Exper. Med. **72**:707 (Dec.) 1940.

thermostromuhr and found that it decreased immediately after partial constriction of the renal artery but that it returned to previous levels after a few minutes. They also found that the blood flow must be reduced by about two thirds to prevent its return to normal levels. Corcoran and Page [16] reported similar results. Alpert and Thomas [17] found that dogs with long-standing hypertension may have normal renal blood flow. Finally, Friedman, Sugarman and Selzer [18] recently published evidence showing that renal ischemia is probably a phenomenon secondary to hypertension. This evidence suggests that reduced blood flow through the kidneys per se is not the primary cause of experimental hypertension, since the hypertension persists in the face of a blood flow which has returned to normal. The only evidence contrary to this hypothesis is the observation of Mansfield and his associates [19] and of Cerqua and Samaan.[20] They increased the renal blood supply by pexis of spleen or omentum to the decapsulated kidney and obtained long-lasting reduction of blood pressure in hypertensive dogs. The reduction lasted until the newly formed collateral circulation was interrupted. This procedure, however, was entirely unsuccessful in relieving hypertension in man.[21]

The observations presented here on renal blood flow in man following supradiaphragmatic splanchnicectomy and sympathetic ganglionectomy are consistent with the hypothesis that some factor other than renal ischemia is the primary cause of hypertension. This is borne out by the fact that there was no increase in effective renal blood flow in those patients whose blood pressure was definitely and persistently reduced by the operation. Two other changes in the dynamics of renal circulation suggest themselves as possible causes for the reduction in blood pressure.

1. The same amount of blood flows through the renal tissue after operation but is distributed more uniformly. We stated in our preceding paper [1] that hypertension might be due to "Irregular distribution of blood to the renal tissue with marked ischemia in one part of the kidney and comparatively normal circulation in other parts." It is conceivable that such ischemic parts might produce an amount of vasoconstrictor substance (? angiotonin) sufficient to produce hypertension. If after operation there were a better distribution of blood to the renal tissue, the tubular excretory mass would be increased, since diodrast would be carried by the blood to a larger number of nephrons. The results of the investigation reported here do not corroborate this hypothesis, because, as has been pointed out,

16. Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Hypertension Due to Constriction of the Renal Artery, Am. J. Physiol. **133**:P 249 (June) 1941.

17. Alpert, L. K., and Thomas, C. B.: Renal Function in Hypertensive Dogs, Bull. Johns Hopkins Hosp. **66**:407 (June) 1940.

18. Friedman, M.; Sugarman, H., and Selzer, A.: The Relationship of Renal Blood Pressure and Blood Flow to the Production of Experimental Hypertension, Am. J. Physiol. **134**:493 (Oct.) 1941.

19. Mansfield, J. S.; Weeks, D. M.; Steiner, A., and Victor, J.: Reduction of Experimental Renal Hypertension by Pexis of Spleen or Omentum on the Kidney, Proc. Soc. Exper. Biol. & Med. **40**:708 (April) 1939.

20. Cerqua, S., and Samaan, A.: Cure of Experimental Renal Hypertension, Clin. Sc. **4**:113 (Dec.) 1939.

21. Abrami, P.; Islin, M., and Wallich, R.: Essai de traitement de l'hypertension artérielle d'origine rénale par la revascularisation chirurgical du rein (néphro-omentopexie), Presse méd. **47**:137 (Jan.) 1939. Goldberg, S.; Rodbard, S., and Katz, L. N.: Increased Collateral Blood Supply to the Kidney in Renal Hypertension, Surgery **7**:869 (June) 1940. Bruger, M., and Carter, R. F.: Nephro-Omentopexy and Nephromyopexy in the Treatment of Arterial Hypertension, Ann. Surg. **113**:381 (March) 1941.

tubular excretory mass was increased in only 3 of our patients, 2 of whom did not have a drop in blood pressure.

2. The pulse pressure within the kidney is increased by the operation, and consequently the diffusion of a vasoconstrictor substance from the renal cells into the blood stream is prevented. The hypothesis that a decreased pulse pressure rather than a decreased renal blood flow might be the primary cause of hypertension has been suggested by Corcoran and Page.[22] Kohlstaedt and Page[23] have shown that when an isolated kidney is perfused with a reduced blood flow no angiotonin is liberated unless the pulse pressure is also reduced. Organs perfused with continuous flow become edematous, and the normal permeability of their cells is altered.[24] It is therefore conceivable that if the pulse pressure in the kidney in human hypertension were reduced the renal cells might allow the diffusion of a vasoconstrictor substance into the blood, producing increased systemic blood pressure.

The fact that in many patients the rate of effective renal blood flow is maintained after operation despite a reduction in blood pressure indicates that the resistance of the renal vessels is probably reduced and that therefore the renal arterioles may be dilated. What would be the effect of this dilatation on the pulse pressure within the renal arterioles? In order to answer this question the investigator must first understand the changes in pulse pressure within the arterial system as the vessels diminish in caliber from the heart to the capillary bed. Pulse pressure is at its maximum in the left ventricle and aorta, and as the arteries diminish in caliber the pulse pressure decreases, until it disappears in the capillaries and veins. It has been shown that the pulse pressure is diminished below the site of a constriction in an artery, such as coarctation of the aorta.[25] It can be assumed, therefore, that the pulse pressure is decreased in the constricted arterioles of the kidney in hypertensive patients. If these constricted arterioles are dilated by the interruption of vasoconstrictor impulses, it follows that the pulse pressure must be increased.

It would seem to be a contradiction that in most of the patients included in this study the brachial pulse pressure, which was high before operation, is decreased postoperatively, whereas the pulse pressure in the renal arterioles is increased. This apparent contradiction, however, is easily understood when one realizes that the preoperative high pulse pressure in the brachial artery was due to increased peripheral resistance. (For a more extensive discussion, see Bradley and Parker,[26] Wilkins and Duncan[27] and Wiggers.[28]) If the peripheral resistance is reduced by removal of vasospasm, the pulse pressure in the brachial artery decreases, whereas it increases in the peripheral arterioles, which have become dilated. Thus

22. Corcoran, A. C., and Page, I. H.: Renal Aspects of Experimental and Clinical Hypertension, J. Lab. & Clin. Med. **26**:1713 (Aug.) 1941.

23. Kohlstaedt, K. G., and Page, I. H.: Production of Renin by Constricting the Renal Artery of an Isolated Kidney Perfused with Blood, Proc. Soc. Exper. Biol. & Med. **43**:136 (Jan.) 1940.

24. Parsons, R. J., and McMaster, P. D.: The Effect of the Pulse upon the Formation and Flow of Lymph, J. Exper. Med. **68**:353 (Sept.) 1938.

25. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta: Report of Three Cases, J. Clin. Investigation **20**:473 (Sept.) 1941.

26. Bradley, S. E., and Parker, B.: The Hemodynamic Effects of Angiotonin in Normal Man, J. Clin. Investigation **20**:715 (Nov.) 1941.

27. Wilkins, R. W., and Duncan, C. N.: The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin, J. Clin. Investigation **20**:721 (Nov.) 1941.

28. Wiggers, C. J.: Basic Hemodynamic Principles Essential to Interpretation of Cardiovascular Disorders, Bull. New York Acad. Med. **18**:3 (Jan.) 1942.

it is apparent how splanchnicectomy can modify the renal circulation by increasing the pulse pressure within the kidney, even though the rate of effective renal blood flow is not increased.

The increase in filtration fraction which was found in 8 of 15 patients five to twelve months after the operation (tables 2 and 3) suggests that arteriolar dilatation may have occurred in the afferent glomerular arteriole, thus increasing the intraglomerular pressure. It was formerly believed by Smith and his associates [29] that the efferent arteriole plays a dominant role in controlling the rate of glomerular filtration. On the other hand, Lamport [30] has recently indicated that the dominant role may be played by the afferent arteriole. Our evidence indicates that both arterioles are probably important in the regulation of glomerular pressure.

Dilatation of the arterioles with concurrent changes in pulse pressure can, of course, occur only when the constriction is due to a reversible spasm which can be removed by an operative procedure, and not when it is due to sclerosis or hypertrophy of the wall. This is borne out by the fact that the best results following operation were obtained in the patients who preoperatively had the greatest degree of vasomotility and the least organic thickening of the systemic arterioles. In evaluating organic arteriolar damage, the measurement of effective renal blood flow and of the wall/lumen ratio of the systemic arterioles in this limited number of patients proved to be at least as valuable as the observation of the eyegrounds or the determinations of urea clearance and urine concentration. Further studies, on a larger number of patients, are needed to decide whether or not the determination of renal blood flow and the measurement of the wall/lumen ratio of the arterioles in biopsy specimens of muscle should be added to the routine preoperative studies of patients with arterial hypertension.

It is fully realized that the conclusions arrived at here are based on the measurement of the blood flow to the renal excretory tissue alone. The total renal blood flow cannot be measured by diodrast clearance, since the blood to the connective tissue is not cleared.[31] It seems unlikely, however, that the connective tissue could play an important role in the production of hypertension.

SUMMARY

Diodrast and inulin clearances were used to measure the effective renal blood flow and filtration rate in 17 patients with arterial hypertension. Measurements were made before bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy and from two weeks to twelve months after the operation. The results indicate that the operation did not change the renal blood flow significantly, even when the blood pressure was reduced. There was a reduction of blood pressure in 8 patients. Constancy of renal blood flow combined with reduced blood pressure suggests decreased vascular resistance and intrarenal arteriolar vasodilatation, with a resultant increase in pulse pressure within the kidney.

The patients with the highest effective renal blood flow, the greatest vasomotility and the least thickening of the systemic arterioles received the most benefit from the operation. It is suggested that the determination of effective renal blood flow

29. Footnote 2. Smith, Goldring and Chasis.[10]

30. Lamport, H.: The Relative Changes in Afferent and Efferent Arteriolar Resistance in the Normal Human Kidney, J. Clin. Investigation **20**:545 (Sept.) 1941.

31. Smith, H. W.: Note on the Interpretation of Clearance Methods in the Diseased Kidney, J. Clin. Investigation **20**:631 (Nov.) 1941.

and the measurement of the wall/lumen ratio of the systemic arterioles in biopsy specimens of muscle might prove to be valuable in the preoperative study of patients with arterial hypertension.

Our results are consistent with the hypothesis that reduced intrarenal pulse pressure, and not renal ischemia, is a causal factor in human hypertension.

The Winthrop Chemical Company, Inc., supplied the diodrast.

ABSTRACT OF DISCUSSION

DR. HAROLD LAMPORT, New York: This paper is especially interesting because it shows the value of hemodynamic considerations in studying hypertension and the application to it of various therapies.

Biopsy of muscle may well become a useful adjunct to hemodynamic studies. It is also likely that the total renal excretory mass may be a good measure of the prospective usefulness in individual cases of splanchnicectomy along with other therapies.

The role of the renal nerves is still not clear. The observations of Smith's group, and of Glaskell, as well as my own observations, have shown that in the kidney of the quadruped there is not a constant vasomotor tone. However, whether this is true of man is not known, and it is possible that man, being a biped, is different, so that in him the renal nerves may be continuously functional. The renal-hypertensive mechanism Dr. Foà has suggested may for that reason be of significance despite the negative animal experiments.

The speculation concerning the relationship of the renal vasomotor nerves to the transmission of the pulse pressure through the blood vessels of the kidney is challenging. While recognizing the intuitive appeal of Dr. Foà's view that preganglionic interruption of the renal nerves may improve nutrition of the kidney by increasing its internal pulse pressure, like Dr. Foà I am aware that scientific proof of this hypothesis has not yet been forthcoming.

It must be remembered that when the blood pressure is much elevated in hypertension the pulse pressure is large, and when the blood pressure declines after successful therapy the systemic pulse pressure also diminishes. Now, if at the same time that the pulse pressure falls systematically the renal arterioles dilate, there is an opposing factor. On the one hand, the systemic pulse pressure is smaller, so that if the arterioles had remained constricted there should be a smaller internal pulse pressure in the kidneys. But, on the other hand, the effect of arteriolar dilatation alone is to increase intrarenal pulse pressure by improving transmission of systemic pulse pressure. When we have two such opposing tendencies, it is impossible to evaluate them without a quantitative estimate of their relative sizes. Unfortunately, I do not know of any pertinent data.

DR. HUGO A. FREUND, Detroit: As clinicians we all agree that it is desirable to know as much as possible about the condition of a patient before subjecting him to as serious and at times as devastating an operation as a splanchnicectomy or any of the other types of operation that have been advised in the various clinics in this country.

Patients frequently ask, "Do you think an operation will benefit me?" Because of the favorable results that I have seen in a number of carefully selected cases, and particularly because Dr. Foà has said that only 50 per cent of his patients have shown favorable results, my associates and I have diligently searched for specific criteria which might form a better basis for selection of patients for operation in whom a favorable outcome might be expected.

It seems to me that the proper basis for the selection for operation of such patients would be an accurate knowledge of the pathologic state of the kidneys. Functional tests of the kidneys, as all physicians know, may give fallacious evidence, and at times reaching a decision might be difficult.

About a year ago one of my associates, Dr. Thomas Horan, began the investigation of the kidneys of animals by making biopsies and later noting what effect the removal of the tissue might have on the parenchyma of the kidney. He first injected trypan blue into the animal and then took a small section out of the kidney at various periods following the vital staining. He was able to show that various stages of renal destruction could be demonstrated; he also was able to prove that such removal of tissue for biopsy had no serious effect on the function of the kidney.

Following this, Dr. Fred H. Cole, of the Urology Department at Harper Hospital, and Dr. Horan performed similar biopsy studies on a group of patients suffering from various types of nephritis and severe essential hypertension. The specimen was removed with a specially devised instrument with which a small core, about 3 mm. in diameter, could be safely taken from the kidney. Histologic study of these specimens was most revealing.

DR. GEORGE E. WAKERLIN, Chicago: It is worth while to point out that there has been experimental work done on the hypertensive dog to show that a reduction in renal blood flow is not necessary for the production of experimental renal hypertension by constriction of the renal arteries. Usually there is a reduction in renal blood flow in these dogs, but it is not a necessary concomitant of experimental renal hypertension, since in some dogs hypertension develops without any reduction in renal blood flow.

I agree with Dr. Lamport that it still has to be demonstrated that a reduction in renal pulse pressure has any relation to the pathogenesis of experimental renal hypertension or clinical hypertension. If a reduction in pulse pressure does play a role, it must act through some chemical mechanism whereby the pressor substance, whatever that may be, is released from the kidney of the patient with essential hypertension.

It is well to emphasize that bilateral splanchnicectomy in the normal dog or human being results in only a temporary reduction in blood pressure. Dr. Foà and his group reported that 50 per cent of their patients showed a reduction in blood pressure at the end of six or twelve months. That is not a long enough time for observation. A minimum period of three years is necessary before results of this sort can be reported as representing positive reductions in blood pressure.

If one examines the vast amount of data concerning the effect of splanchnicectomy on human beings with essential hypertension, one finds that after five years not more than 5 per cent of the patients continue to show a reduction in blood pressure. I am inclined to think that this 5 per cent represents a specific group within the genus of essential hypertension. There undoubtedly are various types of essential hypertension, and I do not feel that bilateral splanchnicectomy is indicated for essential hypertension until such time as we can determine whether the patient is a member of this special group of 5 per cent or one of the 95 per cent.

DR. PIERO FOÀ, Ann Arbor, Mich.: The figures that we have given are group figures; all individual figures were corrected for the average normal body surface of 1.73 square meters. The tubular mass was determined for every patient, and the results indicate that the blood flow is reduced in hypertensive persons also in relation to the mass of their kidneys.

We have presented the hypothesis of the pulse pressure as pure speculation. Unfortunately, there is no means of measuring directly the blood flow or the pulse pressure within the human kidneys, and we have to rely on indirect methods.

No vasomotor tonus seems to exist in normal kidneys. However, abnormal vasoconstrictor stimuli might be present in hypertensive patients.

Dr. Freund stated that the operation is devastating. It certainly is severe, but I do not believe we can call an operation devastating when the patient can leave the hospital and gradually resume his normal activities after only two weeks, and when the average mortality is about 3 per cent.

I agree that some of the tests of renal function, such as determinations of urea clearance, nonprotein nitrogen and urea concentration, are fallacious. Hypertension can be present when renal function is perfectly normal. For this reason we believe that a test of renal circulation, such as the measurement of the blood flow, would tell more about a vascular disease than the aforementioned excretory tests.

The results of renal biopsy are undoubtedly very interesting. We have just completed the study of 350 muscle biopsies in patients who have been followed up to seven years after the operation and have found that there is a striking correlation between the degree of arteriolosclerosis and the results of the operation. The biopsy of muscle might be just as good as a biopsy of the kidney and much easier to perform.

Dr. Wakerlin also objected that the hypothesis of the pulse pressure is purely speculative. I have already answered that objection.

He also stated that splanchnicectomy does not reduce hypertension in Goldblatt dogs. This is to be expected, since the silver clamp on the renal artery cannot be removed by splanchnicectomy. In hypertensive patients, however, the silver clamp is represented by a spasm of the renal arterioles, which can conceivably be relaxed by interruption of the neural pathways carrying vasoconstrictor stimuli.

Only the 22 patients in whom renal blood flow has been studied have been followed for from six to twelve months. A larger series, of 350 consecutive patients, has been followed for periods up to seven years; 50 per cent of them had a significant reduction in blood pressure. The patients were unselected.

ASSOCIATION OF HYDROTHORAX WITH OVARIAN FIBROMA (MEIGS'S SYNDROME)

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T. LLOYD TYSON, M.D.
AND
B. P. WATSON, M.D.
NEW YORK

The mysterious association of fibroma of the ovary with hydrothorax has had infrequent notice in the literature of gynecology and none in that of internal medicine. The earliest recorded case seems to be that reported by Cullingworth [1] in 1879. In 1906 Griffith and Williamson [2] stated that "solid ovarian tumors are often accompanied by hydroperitoneum and sometimes by hydrothorax; this phenomenon has at present received no adequate explanation." In 1937 Meigs and Cass invited renewed attention to this syndrome. Again, in 1939, Meigs [3] emphasized its importance, collecting 15 cases from the literature, 6 from a single hospital. This suggests that the condition is less rare than has been believed. As such cases fall in that no man's land between the internist and the specialist, the significance of the combined thoracic, abdominal and pelvic features may be disregarded. The result of this is too often the denial of life-preserving surgical treatment because of an erroneous diagnosis of inoperable malignant tumor with widespread metastases.

The importance to the internist, as to the gynecologist, of keeping in mind the fact that a benign ovarian tumor may cause hydrothorax as well as ascites and that the simplest of laparotomies uniformly results in complete relief of the thoracic as well as of the abdominal features of the syndrome needs general recognition and emphasis.

REPORT OF A CASE

This interesting, if limited, group was called to our attention by the case of a woman of 75 years, a widow with a history of five normal pregnancies. This patient had always been strong and well, without history of serious acute illness or of surgical operation. Her husband died one year before the first consultation, which was on April 30, 1940. Following her bereavement, the patient did not feel well, suffering from weakness, palpitation, depression and indifference to life. She had no pain and no symptoms referable to the digestive or genitourinary tracts. She noticed occasional edema of the ankles on effort but no loss in weight. She stated that one and a half years before fluid had been aspirated from the right thoracic cavity. She was a slight, pale woman, looking fully her age. The pupils were normal. The fundi revealed moderate arteriosclerotic changes. The mouth and the nares showed no evidence of a focus of infection. The thyroid gland was normal. There was no enlargement of the superficial lymph nodes. The heart was normal in size, position and sounds, without murmur. The rate was 88 and regular; the blood pressure was 140 systolic and 90 diastolic. The brachial vessels were thickened. The breasts were normal. Apart from emphysema and what was interpreted as pleural adhesions at the base of the right lung there were no signs of active disease in the chest. The edge of the liver was just felt

Presented before the Association of American Physicians, Atlantic City, N. J., May 6, 1942.

1. Cullingworth, C. J.: Fibromas of Both Ovaries, Tr. Obst. Soc. London **21**:276, 1879.
2. Griffith, W. S. A., and Williamson, H.: A System of Gynecology, London, Macmillan & Co., 1906, p. 442.
3. Meigs, J. V.: Fibroma of Ovary, Ann. Surg. **110**:731-754, 1939. A complete bibliography may be found in this contribution.

at the margin of the ribs; it was firm but otherwise normal. The gallbladder, the spleen and the kidneys were normal. There was no evidence of free fluid in the abdomen. The reflexes were normal. The temperature was 98.4 F. The weight was 110¼ pounds (50 Kg.). Owing to the age of the patient and the absence of suggestive symptoms, a pelvic examination was deferred.

The chemical survey of the blood with respect to sugar, urea nitrogen, uric acid and chlorides gave negative results. The urine was normal. There was marked secondary anemia. Under the fluoroscope the heart was normal in size and position. There was prominence of the aortic knob, suggesting sclerosis. The right leaf of the diaphragm was judged to be adherent to the wall of the chest and moved little on inspiration. The left leaf was normal in contour and mobility. The pulmonary fields were relatively clear. The hilar shadows were exaggerated with considerable calcification. The electrocardiographic findings suggested a moderate degree of myocardial fibrosis. Roentgenographic study of the entire gastrointestinal tract showed no abnormality.

Three months later, in July, there was considerable edema of both feet. Clubbing of the fingers was noticed. There was persistent anemia of the secondary type. At this time the

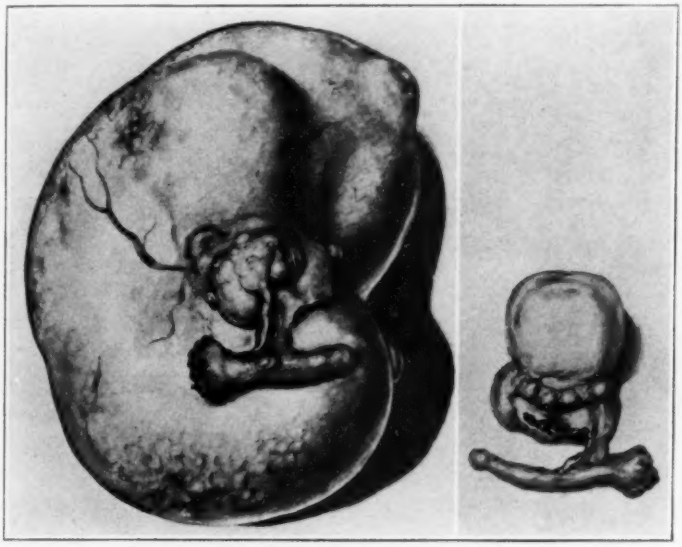

Fig. 1.—Bilateral fibroma with attached ovaries.

signs of fluid at the base of the right lung were unequivocal. The first thoracentesis at our hands produced 1,000 cc. of clear straw-colored fluid. The specific gravity was 1.021. A stained smear of the centrifugate showed a moderate number of red blood cells, 10 to 15 small mononuclears per high power field, and a few large mononuclears. No polymorphonuclear leukocytes were seen, nor cells containing mitoses. Cultures showed no growth. Guinea pig inoculations gave negative results. During the following fourteen months nine aspirations, each of at least 1,000 cc., were performed. Aspiration was done whenever dyspnea or thoracic discomfort and the physical signs of an appreciable amount of exudate demanded the procedure. Careful observation of the temperature during this time revealed no fever.

At first it was thought that we were dealing with a tuberculous process, perhaps a late flaring up of a latent process spreading from the calcified hilar lymph nodes. The absence of pain, of loss of weight and of other evidences of serious infection cast doubt on this preliminary impression.

Meanwhile a deferred pelvic examination revealed a tumor in the right side of the pelvis, about 3 inches (7.5 cm.) in diameter, freely movable between the hands and strongly suggestive of an ovarian enlargement. At no time were there convincing signs of ascites. At

this time, because of the obvious enlargement and firmness of the liver, with local discomfort, the possibility of cancer came to the fore. Rejecting this diagnosis because of the lack of progressive features, we were led to the consideration of Meigs's syndrome. Removal of the ovarian tumor was advised. Owing to the patient's advanced age and the hesitancy of the family, this was postponed for some months, during which the right side of the chest was aspirated repeatedly. Finally, on Feb. 16, 1942, laparotomy was performed by one of us (B. P. W.).

Operation.—With the patient under anesthesia induced by intravenous instillation of a solution of pentothal sodium, the bladder was catheterized and the abdomen prepared and draped. Through a midline incision between the pubes and the umbilicus, the peritoneal

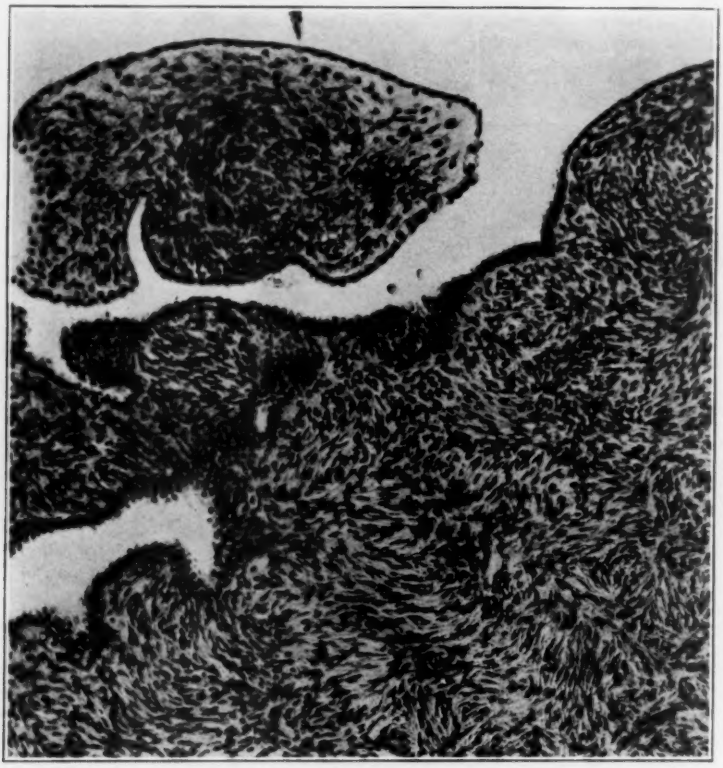

Fig. 2.—Microscopic section through the surface of the mass, showing ovarian tissue.

cavity was opened; 200 to 300 cc. of clear yellowish fluid was aspirated. The large tumor was found to involve the right ovary, which had a narrow pedicle. The left ovary was the seat of a smaller tumor and also had a narrow pedicle. Both pedicles were clamped and the ovaries removed. The pedicles were overstitched with fine catgut. The uterus contained several small subserous fibroid tumors which were not removed. Palpation of the liver revealed slight enlargement but no induration in the substance or on the surface. There were no other intraperitoneal pathologic findings. The abdominal wound was closed in the usual way and healed well. The patient had an afebrile convalescence and was discharged from the hospital two and a half weeks after healing of the wound.

Pathologic Observations.—The specimen consisted of the right ovary and tube and the left ovary and tube.

Macroscopic Examination: The right ovary was round to ovoid and measured 13 by 9.5 by 9 cm. The surface for the most part was smooth with one or two indentations; the

color was ivory with occasional yellow to tan mottling. Numerous dilated veins coursed over the surface. The consistency throughout was firm. In the region of the hilus there was a harder, more lobulated area which was continuous with a small remaining part of what looked like normal ovarian tissue. The fallopian tube was normal in appearance. The left ovary was much smaller in size, measuring 3.5 by 4 by 3 cm. The hilus was very firm and nodular. Projecting from this was a smoother, rounded swelling, similar in appearance to the tumor of the right ovary except that it was more uniform in color and had not the large veins coursing on the surface.

Microscopic Examination: The two tumors were similar in microscopic appearance. The surface was covered with a single layer of cuboidal epithelium which dipped down into deep clefts here and there. Immediately under this epithelial layer were interlacing bands of

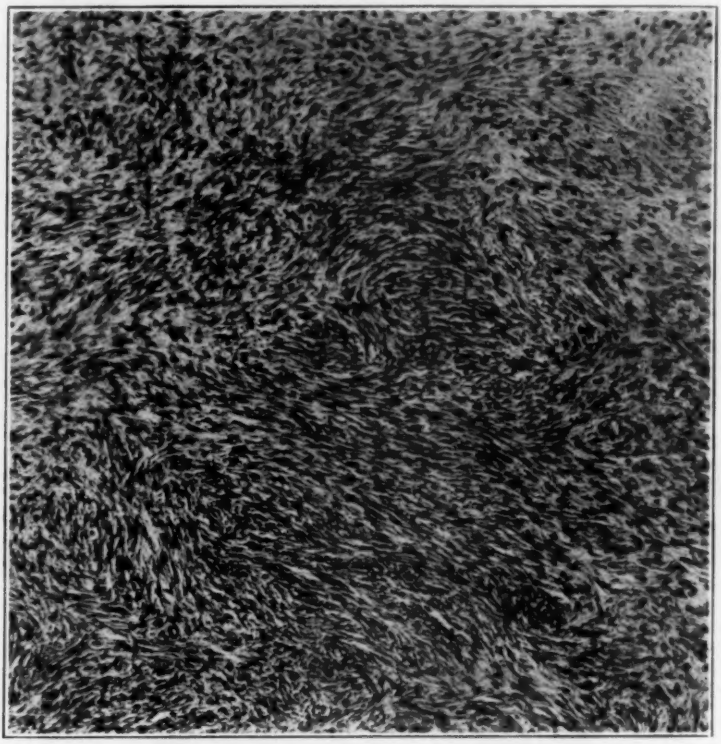

Fig. 3.—Microscopic section through the body of the tumor, showing typical fibroma.

connective tissue which had the general appearance of ovarian stroma. In this were numerous corpora albicantia and corpora fibrosa. Beneath this layer was the tumor proper, which consisted of interlacing bands of fibrous tissue with connective tissue cells and fibrils. The cells were everywhere well formed and exhibited no tendency to rapid proliferation. Cross sections of the fallopian tubes showed the usual folds of mucous membrane covered with a single layer of tall columnar epithelium, which is a normal appearance in the fallopian tubes of a woman of this age.

Pathologic Diagnosis: Bilateral fibroma of the ovary.

Subsequent Course.—Convalescence was uninterrupted. The last aspiration of the chest was done two days before the laparotomy, 1,100 cc. of fluid being removed, with a small residue remaining. Postoperatively, the signs of remaining fluid cleared within a week.

There has been no recurrence of pleural fluid. Several subsequent fluoroscopic and roentgenographic studies of the chest, the last on April 29, 1942, disclosed no trace of pleural exudate. The costophrenic sinus on the right, the previously affected side, was altogether

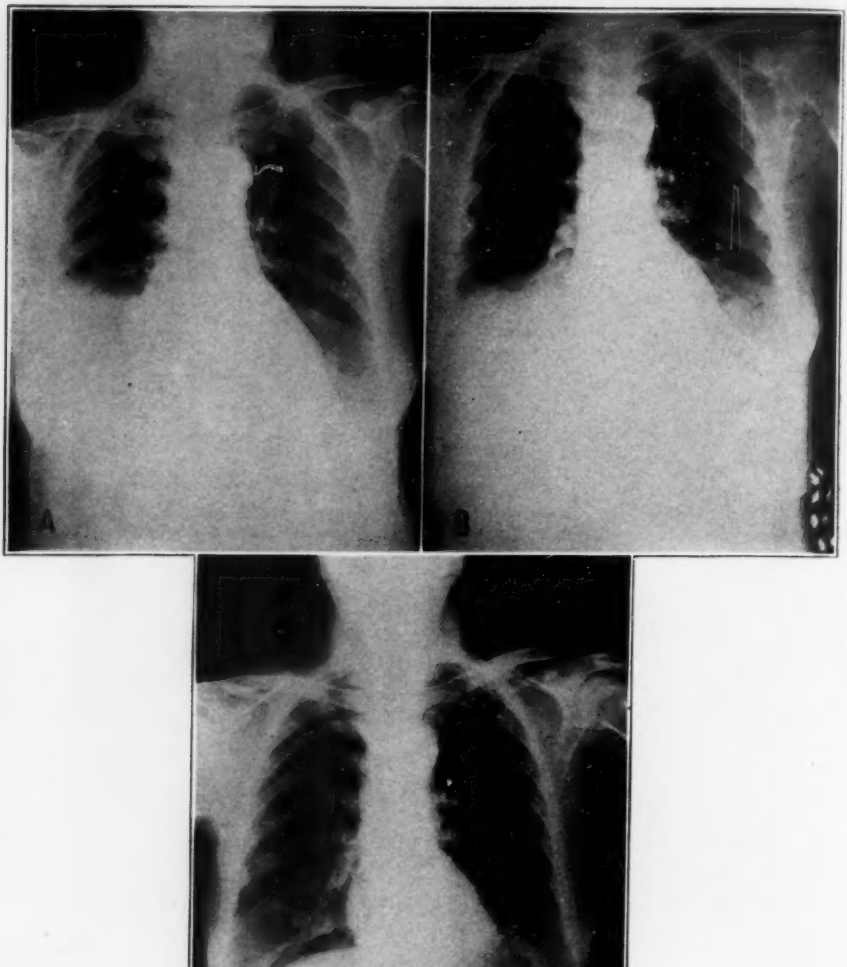

Fig. 4.—Roentgenograms: *A*, the chest before aspiration, showing right hydrothorax. *B*, the chest after aspiration, showing residue of fluid before laparotomy. *C*, the chest ten weeks after removal of the fibromas.

clear. The right leaf of the diaphragm descended normally on inspiration, as did the left. A slight increase in densitiy of the lower lobe of the right lung may be interpreted as the result of repeated and long-continued compression from pleural exudate. Although the

patient was still anemic, the improvement in strength and her feeling of well-being were notable, suggesting the removal of some toxin-forming agent. Of interest and of possible importance was the postoperative change in the liver. This organ, previously large and firm, diminished in size and in hardness, returning to a seemingly normal status within six weeks. This is an item which merits further study in future cases.

ANALYSIS OF REPORTED CASES

In 1939 Meigs collected 15 cases from the literature since the first report of Cullingworth in 1879. The salient statistical points of these together with the case reported here may be given.

The extremes of age were 33 and 75. Our patient was by far the oldest on record. The average age was 51. Ten patients were married; 4 were single; the status of 2 was unrecorded. Seven of the patients had children; 5 were childless; no data in this respect were recorded for 4. In 3 patients the tumor was bilateral; in the rest, equally divided between the right and the left ovary. In 11 patients the effusion in the chest was on the right; in 3, on the left; in 1, bilateral; for 1 the side was not recorded. Three patients had no thoracentesis; 3 had but one, 3 had three; 1, four; 2, five; 1, seven; our own patient had 11, while for 2 there were "repeated" aspirations. Abdominal paracentesis was not required in 10 patients; 4 had but one; 1 was tapped four times, and 1 nine times. Ascites, therefore, seems less of a feature than hydrothorax.

At operation the amount of fluid in the peritoneal space varied from a small amount to 6 to 8 quarts (5.5 to 7.5 liters). In most cases it was less than 1,000 cc. The duration of symptoms was comparatively short in the average case. In all cases both the thoracic and the abdominal fluid vanished postoperatively. There was one death with necropsy. No pathologic changes in the pleura were described. The only abnormal finding in the chest was compression of the lung from long-standing and apparently neglected hydrothorax.

Thus far there has been no satisfactory explanation of the association of ovarian fibroma with hydrothorax and ascites. The possibility of an abnormal communication between the two serous cavities may be dismissed, since the amount of fluid in one cavity is not influenced by removal of fluid from the other. That a low level of serum protein is concerned seems unlikely. In the 2 cases in which the serum proteins were estimated no important variation from the normal was found. Again, if accumulations of fluid in the serous cavities were a result of diminution in serum proteins, edema of the subcutaneous tissues should be present. Although noted in our case, it was slight and transitory, while in most reported cases it was not observed.

Meigs mentioned the so-called "alarm reaction" of St. Karady, Brown and Selye. In rats these observers found that repeated, even minor traumas—physical or chemical—cause a resistance to be built up which lasts two or three months. With continuing action of the noxious agents, the animals lose their resistance and show decline in the output of urine, retention of water and at times collection of fluid in the pleural and peritoneal cavities shortly before death from toxicosis or shock. This being granted, it is difficult to understand why other ovarian tumors generally fail to give rise to hydrothorax.[4] For the present one must be content with the general statement that an ovarian fibroma in some manner wholly unknown

4. Rarely other pelvic tumors give rise to hydrothorax. An example is found in the case of Salmon in which a large uterine fibroid with intraligamentous extension and follicular cysts of the ovaries was present with 300 cc. of fluid in the peritoneum and 700 cc. of bloody fluid in the chest. After removal of the tumor growths there was no recurrence of the hydrothorax.

increases the permeability of the pleura. Whether reflexively, by the production of toxins that circulate with the blood, by allergic effects or by hormonal influence is altogether a matter of speculation.

SUMMARY

Sixteen cases are on record of the association of hydrothorax and ovarian fibroma. Such cases probably are more common than appears. Because they fall within two fields—internal medicine and gynecology—many are unrecognized or diagnosed erroneously as malignant tumor with metastases.

The cause of the association of ovarian fibroma and hydrothorax is quite unknown.

Removal of the fibroma results in complete and permanent cure of the hydrothorax.

Heretofore recognized, at least in medical writings, only by the gynecologist, this syndrome should be considered by the internist in every case in which hydrothorax is encountered in a woman beyond the age of 30. This is especially needful if recurrent hydrothorax is not attended by fever, cachexia or loss of weight.

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INCIDENCE AND CAUSES OF HYPERPROTEINEMIA

A STUDY OF 4,390 CASES

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We had observed 2 cases of relatively common diseases associated with hyperproteinemia (a case of subacute bacterial endocarditis and a case of cirrhosis and primary carcinoma of the liver).[1] The simultaneous presence of 2 patients with the supposedly rare condition of hyperproteinemia, lying side by side, in a small (200 bed) semiprivate hospital prompted a study of the incidence and the causes of this condition in our climate and locality. This communication presents the results of a clinical-experimental investigation of this subject in a larger series of patients than has hitherto been reported.

LITERATURE

Jeghers and Selesnick,[2] summarizing the determinations of total plasma protein made by the clinical laboratories of the Boston City Hospital, reported that the incidence of total protein over 8 Gm. per hundred cubic centimeters was 0.2 per cent of 557 determinations in 1934, 1.19 per cent of 526 determinations in 1935 and 2.4 per cent in 1936. These figures were compared with those for total protein less than 6 Gm. per hundred cubic centimeters in the same series of cases, 69.5 per cent, 56.4 per cent and 49.2 per cent, respectively. The increased incidence of high protein values in 1935 and 1936 reflected a greater number of blood protein determinations made specifically for hyperproteinemia in patients in whom multiple myeloma (a disease in which hyperproteinemia is common) was suspected. This series represents determinations presumably made only when abnormal levels of blood protein were suspected and as such may not present a true general incidence. Shuman and Jeghers[3] in a single medical service in the Boston City Hospital during April and May of 1939 found, in 320 successive determinations of blood

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1. Cardon, L., and others: To be published.

2. Jeghers, H., and Selesnick, S.: Hyperproteinemia: Its Significance, Internat. Clin. **3**: 248-279 (Sept.) 1937.

3. Shuman, H. H., and Jeghers, H.: Value of Routine Blood-Protein Determinations, New England J. Med. **222**:335-339 (Feb. 29) 1940.

proteins by the Kagan falling drop method, only 1 instance of hyperproteinemia (in a case of multiple myeloma). Bing [4] found 7 hyperglobulinemic serums (as determined by routine formaldehyde-gel tests ["formal"-gel tests]) among 3,697 serums examined. He concluded that in Denmark hyperglobulinemia is usually found only in patients with multiple myeloma or chronic infections. None of these series represents random sampling from all patients admitted to a hospital.

MATERIALS AND PROCEDURE

The recent introduction of the falling drop method has made possible routine, rapid and accurate determination of the total serum protein concentration on a large number of serums. To obtain patients with hyperproteinemia for detailed study, and to determine the incidence of this condition and the pathologic states associated with it, total protein was determined by the Kagan falling drop method [5] on 4,370 serums submitted to the department of serology of the Cook County Hospital for routine Kahn and Wassermann tests. This was done by the method of random sampling but did not include serum samples from the three divisions of the hospital: that for tuberculous patients, that for patients with contagious diseases and the pediatrics division. The number of patients admitted to these three departments constitute only 20 per cent of the total number admitted. More than half of the patients with tuberculosis are admitted first to the general hospital and consequently are included in this survey.

When a high level of total protein was discovered by the falling drop method, a fresh specimen was obtained from the patient for chemical determination of the concentrations of total protein, albumin and globulin and special tests as indicated in table 1. While we had no control over the technic of obtaining the original samples which were sent to the serologic laboratory, all subsequent samples of blood drawn by us were obtained with a minimum of venous stasis. It has been shown by Rowe [6] and others that the venous stasis produced by the application of a tourniquet for even a few minutes may result in an increase of serum proteins in the constricted extremity due to a transfer of water from blood to the tissues.

The frequency of lymphogranuloma venereum in the Cook County Hospital made it advisable to do the Frei test whenever possible. This test alone when positive may disclose the true cause of hyperproteinemia which might be otherwise attributed to another condition. In any case in which the Frei test was not performed, the absence of lymphogranuloma venereum could not be assumed with certainty.

RESULTS

Fifty-four cases in which the value for total serum protein was above 8.5 Gm. per hundred cubic centimeters were found in the examination of the serums of 4,370 patients by the falling drop method, giving an incidence of hyperproteinemia of 1.2 per cent. Of this series, obtained by random sampling, only 18 cases could be studied adequately. Seventeen additional cases in which hyperproteinemia had been noted were called to our attention by staff members of the hospital, and 3 cases were added from our private practice, making a total of 38 cases studied adequately. Our special interest in the relationship of hyperproteinemia to disease of the liver was known to our colleagues and explains the greater number of cases of hepatic disease referred to us.

In table 1 all of the pathologic conditions noted in each patient are given. Where one pathologic condition known to be a frequent cause of hyperproteinemia was found, we assumed that it was the main or only cause in that particular case. The conditions that were found to be associated with hyperproteinemia, listed in table 1, are summarized and classified in table 2.

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4. Bing, J.: Formolgel Reaction and Other Globulin Reactions, Acta med. Scandinav. **91**: 336-356, 1937; Hospitalstid. **80**:113-128 (Feb. 2) 1937.

5. Kagan, B. M.: Simple Method for the Estimation of Total Protein Content of Plasma and Serum: Falling Drop Method for the Determination of Specific Gravity, J. Clin. Investigation **17**:369-372 (July) 1938.

6. Rowe, A. H.: Effect of Venous Stasis on the Proteins of Human Blood Serum, J. Lab & Clin. Med. **1**:485-489, 1915.

As described by other workers, the increase in total protein concentration in our instances of "true" hyperproteinemia was found to be correlated with an increase in globulin concentration and usually with a concomitant decrease in albumin concentration.

COMMENT

Several major difficulties arose in the classification of our cases. We were first faced with the unsettled problem of eliminating hemoconcentration as the cause of increased concentration of serum proteins. Hemoconcentration [7] resulting from shock, venous stasis or dehydration has been given as one of the commonest causes of (apparent) hyperproteinemia. A study of the literature reveals that in many of the cases of hyperproteinemia reported these factors were not sufficiently taken into consideration. This fact may in part account for the wide variety of clinical conditions with hyperproteinemia hitherto reported. It is generally known that the state of hydration cannot be determined clinically with any degree of certainty. The usual clinical signs and symptoms may not become manifest until 6 per cent or more of the body weight in water has been lost. The exact amount of fluid that must be lost to produce apparent changes in the concentration of the blood is not yet known. According to the concept of Gamble,[8] the interstitial fluid, which is three times the volume of the plasma, serves as a reservoir to maintain the fluid and electrolyte balance of the circulating blood. Schiff [9] regarded the dehydration of the plasma and that of the interstitial tissues as running parallel, and Gregerson and Stewart [10] stated that work now in progress in their laboratories proves the volume of plasma is not independent of the quantity of interstitial fluid even with moderate changes in the total volume of extracellular fluid. We were interested in the state of hydration only as it affected the hydration of the blood. A patient may have a considerable increase in the total amount of available fluids with generalized edema, as in nephrosis, and yet manifest hemoconcentration.

The laboratory methods recently developed to determine the state of hydration are also fraught with misleading factors. Red blood cell and hematocrit determinations are of value only in the absence of anemia or polycythemia. Determinations of specific gravity and total serum protein must be discounted in the presence of pathologic conditions known to be associated with hypoproteinemia or hyperproteinemia. In chronic states of prolonged dehydration, the red blood cell count and the serum protein value tend to fall as a result of destruction of the red blood cells and serum proteins.[11] Since depletion of sodium is a significant factor in dehydration, it has been thought that the water loss can be computed from the sodium concentration in the blood plasma. However, Simeone and Sarris [12] stated that the total base of the blood plasma may remain normal in the presence of moderately severe dehydration if renal function is unimpaired. Nevertheless, low serum sodium may be definite evidence of dehydration. The determination of

7. Mandelbaum, H.: Syndrome of Hemoconcentration, Internat. Clin. **2**:112-142 (June) 1936.

8. Gamble, J. L.: Extracellular Fluid, Bull. Johns Hopkins Hosp. **61**:151-173 (Sept.) 1937.

9. Schiff, E.: Das Exiccoseproblem, Ergebn. d. inn. Med. u. Kinderh. **35**:519-603, 1929; Klin. Wchnschr. **8**:1105-1109 (June 11) 1929.

10. Gregerson, M. I., and Stewart, J. D.: Simultaneous Determination of Plasma Volume with T-1824 and "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**: 142-152 (Jan.) 1939.

11. Best, C. H., and Taylor, N. B.: The Physiological Bases of Medical Practice: A University of Toronto Text in Applied Physiology, ed. 2, Baltimore, Williams & Wilkins Company, 1939, p. 32.

12. Simeone, F. A., and Sarris, S. P.: Simple Method for Determination of Serum Protein, J. Lab. & Clin. Med. **26**:1046-1052 (March) 1941.

TABLE 1.—*Findings in Thirty-Eight Cases in Which Hyperproteinemia Was Present* *

Patient and Age	Sex and Color	History and Physical Findings	Date	Dehydration: Clinical	Dehydration: 24 Hr. Urine, Cc.	Dehydration: Hematocrit Reading	Red Cell Count	Hemoglobin, %	Serum Protein: Total by Kagan Technic, Gm. per 100 Cc.	Serum Protein: Total Chemically Determined, Gm. per 100 Cc.	Serum Protein: Albumin, Gm. per 100 Cc.	Serum Protein: Globulin, Gm. per 100 Cc.	Serum Protein: A.-G. Ratio	Takata-Ara Test	Formaldehyde-Gel Test	Sedimentation Rate, Mm.: Original	Sedimentation Rate, Mm.: Corrected	Frei Test	Kahn Test	Wassermann Test	Course	Diagnosis
1	M	Chronic alcoholism, hemoptysis, melena, ascites, dependent edema	4/25	None	.....	29	3,350,000	62	8.25	8.78	2.05	6.73	0.31	4 plus	4 plus	125	87	Neg.	2 plus	Ac †	Discharged with condition unchanged	Cirrhosis
47	W		5/ 5	.....	.....	..	.....	..	8.94	8.47	2.19	6.28	0.35	4 plus	4 plus	123	87					
			5/12	.....	.....	..	.....	..	8.00													
2	M	Alcoholism (?), progressive painless jaundice	12/19	None	.....	..	4,280,000	85	....	7.50	3.35	4.15	0.81	.....	.....	...	..	.....	Neg.	....	Discharged with condition unchanged	Cirrhosis
48	W		12/26	.....	.....	..	.....	..	....	10.04	3.75	6.29	0.60									
			12/30	.....	.....	..	.....	..	....	10.04	3.75	6.29	0.60									
3	F	Alcoholism, jaundice, enlargement of liver and spleen, ascites	1/22	.....	.....	..	1,980,000	47	....	9.38	2.87	6.51	0.44	.....	.....	...	..	.....	4 plus	Neg.	Died; autopsy performed	Cirrhosis
27	N																					
4	M	Alcoholism, chills, fever, jaundice, enlargement of liver	.....	None	.....	..	5,190,000	94	....	8.71	5.02	3.69	1.82	.....	.....	...	..	...	Neg.	....	Complete recovery	Acute hepatitis
34	W		11/26	.....	.....	..	.....	..	....	9.38	5.62	3.76	1.49									
			12/ 9	.....	.....	..	.....	..	7.81	7.37												
5	F	Diabetes, jaundice, vomiting, diarrhea, enlargement of liver	3/29	None	.....	..	4,380,000	72	....	8.53	3.35	5.18	0.65	.....	.....	...	..	.....	Neg.	....	Discharged improved	Cirrhosis
59	W		4/ 7	.....	.....	..	.....	..	....	8.53	3.75	4.78										
6	M	Alcoholism, painless jaundice, enlargement of liver	2/ 3	None	.....	..	4,450,000	87	....	6.71	3.7	3.01	1.23	.....	.....	...	..	.....	Neg.	....	Discharged improved	Cirrhosis
31	W		2/10	.....	2,200	..	.....	..	....	9.38	4.94	4.44	1.11									
			2/24	.....	.....	..	.....	..	8.59	7.9												
			4/ 1	.....	.....	..	.....	..	....	6.62	4.21	2.41	1.75									
7	M	Alcoholism, a condition which on several previous admissions was diagnosed cirrhosis of liver, edema of ankles	4/17	None	.....	..	4,360,000	82	....	9.38	5.21	4.17	1.25	.....	.....							
47	W		4/21	.....	.....	36	.....	..	7.84	....	....	....	....	1 plus	Neg.	...	..	.....	Neg.	....	Discharged with condition unchanged	Cirrhosis
			4/24	.....	.....	..	.....	..	....	8.55	6.12	2.23	2.74									
8	M	Alcoholism, progressive enlargement of liver, severe cachexia, abdominal pain, diarrhea, enlarged nodular liver	3/ 8	None	.....	..	4,800,000	62	....	13.30	3.53	9.77	0.36	.....	.....	...	..	.....	Neg.	....	Exploratory laparotomy; biopsy of liver; no autopsy	Cirrhosis of liver with primary carcinoma
	W		3/13	.....	.....	..	.....	..	....	8.06	2.79	5.27	0.53									
			3/15	.....	.....	..	.....	..	....	9.50	3.75	5.75	0.65	2 plus	4 plus	105						
9	F	Painless jaundice; liver not palpable on 7/8 but enlarged on 7/16	7/ 8	None	.....	..	4,050,000	68	....	8.71	5.02	3.69	1.36	.....	.....	...	..	.....	.....	.....	Discharged improved	Catarrhal jaundice
20	N		7/16	.....	.....	..	.....	..	....	8.53	4.94	3.59	1.38	1 plus	2 plus	100						
			7/19	.....	.....	34	.....	..	7.80	7.33	5.19	2.14	2.42	.....	.....	...	..	Neg.	Neg.			
10	F	Long history of lympho-	3/18	Marked	.....	..	.....	..	10.33	9.44	2.0	7.44	0.27	4 plus	4 plus	130	86	4 plus	Neg.	....	Died on 4/7/41	Lymphogranuloma
39	N	granuloma venereum with rectal stricture and granulations; admitted to hospital in coma	3/19	.....	.....	36	.....	..	....	10.13	2.47	7.66	0.32	.....	4 plus							venereum; dehydration
			3/21	.....	.....	..	3,150,000	60														
			4/ 1	.....	.....	..	.....	..														

39	N	granuloma venereum with rectal stricture and granulations; admitted to hospital in coma	3/19 3/21 4/ 1	.....	.....	25	.....	..	....	10.13	2.47	7.66	0.32	.....	4 plus							Granuloma venereum; dehydration
11 44	M W	Atrophic arthritis 9 yr.; lymphogranuloma venereum 12 yr., with rectal involvement; stricture 8 yr.; colostomy	4/16 4/21 5/13	None	....	 25	 3,430,000	 38	.... 0.56	11.44 9.50 8.74	4.37 3.85 2.95	7.07 5.65 5.79	0.62 0.68 0.51	.... 4 plus	.... 4 plus	... 130	.. 86	..... 4 plus	.... Neg.	....	Colostomy; blood transfusion; slight improvement	Lymphogranuloma venereum; atrophic arthritis
12 27	F W	Lymphogranuloma with rectal stricture and colostomy, 1 yr.	4/27 5/ 2 5/ 5	None	....	.. 39 ..	....	84	8.83 8.56 8.94	.... 8.47	.... 4.02	.... 4.45	.... 0.90	Neg. 2 plus	3 plus 2 plus	... ...	.. ..	..... 4 plus	.... Neg.	....	Colostomy; discharged improved	Lymphogranuloma venereum
13 50	M W	Ulcers of glans penis with secondary malignant degeneration	12/19 12/31	None	1,200	.. ..	....	.. ..	9.87	.... 9.50	.... 3.09	.... 0.41	.... 0.48	.....	.....	...	..	4 plus	Neg.	....	Cystotomy; discharged	Lymphogranuloma venereum; carcinoma of penis
14 46	F N	Chronic stricture of rectum; admitted to hospital because of obstructive jaundice	1/31 2/ 4 2/18 4/30 6/19	None	1,800	.. ..	3,290,000	63	.... 8.73	8.98 9.38 7.99 9.90 9.22	3.27 3.16 3.16 3.31 5.07	5.71 6.22 4.83 6.59 4.15	0.57 0.51 0.66 0.50 1.22	..... 4 plus	..... 4 plus	... ...	.. ..	..... 4 plus	Neg.	....	Choledochoduodenostomy; biopsy of liver	Lymphogranuloma venereum; obstructive jaundice
15 24	M N	Ulcers of penis with inguinal adenopathy (buboes)	11/21	None	.....	..	.....	..	9.45	....	....	....	....	.....	.....	...	..	4 plus	Neg.	Neg.	Discharged recovered	Lymphogranuloma venereum
16 49	F N	Moderate edema of hands and feet, frequency and burning on urination	3/21 3/25 4/ 9 4/10 4/21	None	..... 1,500	.. 53 25	..... 3,290,000	.. 59	.... 9.63 .... 8.42 8.42	8.53 10.15 6.64 7.46	3.65 3.61 3.16 2.16	4.88 6.54 3.48 5.30	0.75 0.55 0.91 0.41	..... 4 plus ..... 4 plus	..... 4 plus ..... 4 plus	... 120 133	.. 89 88	.... Neg.	.... 3 plus .... 1 plus	.... Ac .... Neg.	Discharged improved	Chronic pyelonephritis, latent
17 55	M W	Epigastric pain, 30 lb. (13.5 Kg.) loss, frequency and burning on urination 3 mo. duration	4/29 5/14 5/22 6/ 9 6/20	None	....	.. 19 .. 17 22	2,080,000	34	.... 9.45 8.35 7.63 7.45	8.53 .... 7.45	2.81 .... 3.53	5.72 .... 3.80	0.49 .... 0.96	..... 4 plus 4 plus 3 plus 2 plus	..... 4 plus 4 plus 2 plus 2 plus	... 150 .. 150 150	.. 92 .. 90 90	..... Neg. 	.... Neg. Neg. 	....	Nephrectomy; discharged recovered	Calculus; pyonephrosis
18 18	F Indian	Low grade fever; 15 lb. (6.8 Kg.) weight loss 4 mo.; orange-sized, tender, cystic mass in pelvis	6/16 6/20 6/24 6/26 7/25	None	....	.. .. .. 30 36	3,040,000	43	.... 10.25	9.38 10.04 12.76 10.10	3.65 3.50 4.68 3.45	5.73 6.54 8.08 6.65	0.64 0.54 0.58 0.52	.... 4 plus 4 plus	.... 4 plus 4 plus	... ... 130 110	 90 	.... Neg. 	.... Neg. 	....	Colpotomy; purulent drainage; improved	Pelvic cellulitis (nonspecific)
19 76	M W	Diabetes 20 yr., infected gangrenous leg 8 wk., diabetic acidosis	4/28	2 plus	.....	..	4,200,000	90	....	10.0	3.96	6.08	0.65	.....	.....	...	..	.....	Neg.	....	Died; autopsy	Moist gangrene of leg with secondary infection; diabetes

* The values shown were obtained by standard laboratory methods: the sedimentation rate by the Westergren[34] method, the hematocrit by the Wintrobe[35] method (corrected by the method of Plass and Rourke[36]), the Takata-Ara test according to the technic of A. B. Ragins (Value of the Takata and Ara Reaction as Diagnostic and Prognostic Aid in Cirrhosis of Liver, J. Lab. & Clin. Med. **20**: 902-913 [June] 1935), the formaldehyde **gel reaction according to the method of Klein and others (Klein, B.I.; Levinson, S. A. and Stulik, C. E.: Formal-Gel Test During Rheumatic Fever of Childhood: Comparison with Sedimentation Rate and Weltmann Reaction, J. Pediat. 18: 337-356 [March] 1941)**, the Frei test using chick embryo antigen, the total protein determinations by the Kagan[5] falling drop technic and the standard micro-Kjeldahl method.

† **Ac means anticomplementary.**

TABLE 1.—*Findings in Thirty-Eight Cases in Which Hyperproteinemia Was Present* *—*Continued*

Patient and Age	Sex and Color	History and Physical Findings	Date	Dehydration: Clinical	Dehydration: 24 Hr. Urine, Cc.	Dehydration: Hematocrit Reading	Red Cell Count	Hemoglobin, %	Serum Protein: Total by Kagan Technic, Gm. per 100 Cc.	Serum Protein: Total Chemically Determined, Gm. per 100 Cc.	Serum Protein: Albumin, Gm. per 100 Cc.	Serum Protein: Globulin, Gm. per 100 Cc.	Serum Protein: A.-G. Ratio	Takata-Ara Test	Formaldehyde-Gel Test	Sedimentation Rate, Mm.: Original	Sedimentation Rate, Mm.: Corrected	Frei Test	Kahn Test	Wassermann Test	Course	Diagnosis
20 8	M W	Generalized erythema, pains in joint, purulent discharge from ears, bloody urine, fever	11/10 11/18	None	....	.. ..	2,800,000	54 ..	....	9.38 10.04	4.94 5.26	4.44 4.78	1.11 1.10	.....	.....	... ...	.. ..	.....	Neg.	....	Complete recovery	Scarlet fever; otitis media; arthritis; hemorrhagic nephritis
21 11	M W	Generalized erythema, strawberry tongue, desquamation, tender swollen joints	5/ 8 5/12	None	....	.. 41	3,780,000	75 ..	9.56 9.01	.... 7.87	.... 3.64	.... 4.23	.... 0.86	....	....	... 110	.. 94	.....	Neg.	....	Complete recovery	Scarlet fever; acute arthritis
22 38	F W	Prolonged fever, purulent discharge from ear, erysipelas	5/ 6 5/ 9	None	....	.. 30	3,500,000	67 ..	8.87 7.35	....	....	....	....	..... Neg.	..... Neg.	... 100	.. 52	.....	.... Neg.	Neg.	Complete recovery	Erysipelas; otitis media
23 35	M N	Chills, fever, lumbar pain; urgency, frequency, burning on urination; dryness of mucous membranes	4/16 4/18 4/22 4/23 4/25	4 plus 4 plus 2 plus None None	....	.. 49 33	..... 3,700,000	.. 64	9.70 10.50 8.05 7.84 7.22	....	....	....	....	....	.... Neg.	... 95 ... 120 ...	.. 92 ... 94 ...	.....	....	Neg. Neg. Neg. Neg.	Intravenous injection of fluids; sulfonamide compounds; complete recovery	Acute pyelonephritis; dehydration
24 59	M N	30 lb. loss in 2 yr.; cough, dysphagia, fever, abdominal distention, emaciation; serum sodium low (128 mEq.)	4/ 9 4/11 4/16	4 plus	....	50	4,000,000	62	10.1 8.87 9.01	.... 8.49	.... 2.34	.... 6.15	.... 0.38	....	....	 85	 85	.....	Neg.	....	Died; autopsy obtained	Bilateral pulmonary tuberculosis; tuberculous peritonitis; dehydration
25 27	F N	Cough, loss of weight, night sweats, acid-fast bacteria in sputum, emaciation; roentgenogram of chest: infiltration of left lung	3/26 3/30 4/ 7 4/28 5/12	None	1,000 900	.. 20 34 .. 31	....	.. ..	8.73 9.11 9.15 9.60 9.38	.... 8.42 .... 8.16	.... 2.90 .... 3.16	.... 5.52 .... 5.0	.... 0.55 .... 0.63	....	....	... ... 105 115	.. .. 70 82	..... Neg.	.... Neg.	....	Condition unchanged; transferred to hospital for tuberculous patients	Pulmonary tuberculosis
26 56	M W	Old history of rheumatic heart disease; cough, fever, symptoms of congestive heart failure, petechiae, clubbing of fingers, enlargement of liver and spleen	3/ 2 3/ 8 3/15 3/25 4/22 10/25 11/11	..... Moderate ..... at times	....	.. ..	3,200,000	50	....	.... 10.90 8.12 12.10 8.06 8.78 7.84	.... 4.70 3.84 4.33 4.11 4.09 3.86	.... 6.20 4.28 7.77 3.95 4.69 3.98	.... 0.76 0.90 0.56 1.04 1.15 0.97	.... Neg. ..... Neg. Neg.	..... Neg. ..... 1 plus ..... 1 plus	110 129 ... ... 125 59	.. ..	Neg.	Neg. Neg.	Ae Ae	Concomitant hyperthyroidism; improved after thyroidectomy Died; autopsy	Endocarditis lenta (persistently negative blood cultures) Hyperthyroidism confirmed by histologic study
27 15	F N	History of severe prolonged rheumatic heart disease; admitted to hospital in coma	4/22	4 plus	.....	..	.....	..	10.04	....	....	....	....	.....	.....	..	..	.....	Neg. 3 plus	.... ?	Died 24 hr. after admission; autopsy Complete	Ulcerative endocarditis; cerebral emboli Malaria

27 15	F N	*History of severe prolonged rheumatic heart disease; admitted to hospital in coma*	4/22	4 plus	.....	..	.....	..	10.04	....	....	....	....	.....	.....	..	..	.....	Neg.	....	Died 24 hr. after admission; autopsy	Ulcerative endocarditis; cerebral emboli
28 21	M W	Chills and fever coming on 4 days after appendectomy; malarial parasites found in peripheral blood	10/ 3 10/10 10/30	None	.....	..	.....	..	....	8.8 7.6 6.7	4.2 3.9 5.1	4.6 3.7 1.6	0.91 1.05 3.19	.....	.....	...	..	.....	3 plus 1 plus Neg.	? Neg. Neg.	Complete recovery on quinine	Malaria
29 31	F N	Severe anemia, weakness, arthritic pains 6 yr.; moderate jaundice (fragility test normal); enlargement of liver and spleen; sternal marrow normal	4/17 4/22	None	530	.. 27	1,000,000 2,500,000 (after transfusions)	10 40	8.46	8.98	4.86	4.12	.... 1.18	.....	.....	...	..	.....	4 plus 4 plus	4 plus 4 plus	Repeated blood transfusions; antisyphilitic therapy	Anemia of undetermined cause; syphilis; hepatitis (?)
30 55	M W	Severe progressive pain in back and long bones; weakness; 30 lb. weight loss in 6 mo.	9/16 9/18 10/ 6 p. m.	None	.....	.. ..	..... 2,270,000	.. 45 ..	.... 9.70	10.25 11.44 10.36	2.75 3.55 2.90	7.50 7.89 7.46	0.36 0.45 0.39	....	....	... ...	.. ..	....	Neg. Neg.	Ac	Progressively downhill course; died; autopsy	Multiple myeloma
31 8	F N	Marked emaciation; defects in bones; negative Mantoux test; roentgenogram of chest: diffuse miliary lesions	..... 11/15 12/31	....	....	.. .. ..	....	.. .. ..	....	9.76 8.71 8.17	4.62 5.21 4.43	5.14 3.50 3.74	0.90 1.49 1.18	.....	.....	...	..	.....	....	....	.....	Boeck's sarcoid
32 70	M N	Obstipation and continuous vomiting 2 wk. prior to admission; skin and mucous membranes dry; patient extremely cachectic	1/21 1/29	4 plus None	.....	..	5,300,000 4,100,000	98 70	13.0	.... 7.41	.... 4.50	.... 3.11	.... 1.38	....	....	... ...	.. ..	....	.... Neg.	....	Intravenous injection of fluids; discharged; complete recovery	Dehydration from prolonged vomiting, cause unknown
33 56	F N	Admitted to hospital in diabetic coma; air hunger; acetone breath; urine showed albumin (4 plus) and sugar (4 plus)	4/22 4/28	4 plus None	.....	..	4,570,000	.. ..	9.0 7.49	8.98	6.25	2.73	2.29	.....	.....	...	..	.....	Neg.	....	Intravenous injection of fluids; insulin; discharged; complete recovery	Diabetic coma; dehydration
34 21	F N	Chills; prolonged fever; bleeding of gums; generalized adenopathy; heterophile agglutination negative for infections mononucleosis	1/15 1/22 1/24	None	.....	.. ..	4,100,000	80 ..	8.81 8.71	.... 8.71	.... 6.55	.... 2.16	.... 3.03	....	....	... ...	.. ..	....	.... Neg.	....	Complete recovery	Cryptogenic fever; infectious mononucleosis (clinical)
35 20	F N	Bilateral cervical adenopathy 4 mo.; epistaxis 2 mo.; roentgenogram of chest negative	3/25 3/27	None	.....	40 ..	3,970,000	62 ..	8.73 8.80	8.73 8.80	.... 8.14	.... 4.57	.... 3.57	..... 1.28	..... 4 plus	... 4 plus	.. 70	....	.... Neg.	.... Neg.	Refused biopsy of glands of neck; discharged	Hodgkin's disease (?); tuberculosis (?); lymphosarcoma (?); infectious mononucleosis (?)
36 38	F N	Alcoholism; admitted to hospital in status epilepticus; deep coma; temp. 106 F.	4/16 4/22	4 plus None	.....	..	.....	..	9.56	....	....	....	....	....	..... Neg.	... 80	.. ..	....	2 plus 2 plus	Neg.	Improved; transferred to psychopathic hospital	Chronic alcoholism with mental deterioration
37 13	M N	Large chronic ulceration of scrotum; biopsy of ulcer showed nonspecific granulation tissue	3/18 3/19 3/24 4/28	None	..... 1,700 1,800	.. 40 36 ..	 3,600,000	 58	9.32 9.23 8.48 8.49	.... 9.16 8.79	.... 3.75 3.61	.... 5.41 5.18	.... 0.69 0.70	4 plus 4 plus ..... 4 plus	4 plus .... 4 plus	... 132 101 ...	.. 110 78 ..	..... Neg.	Neg.	....	Slowly improved on zinc peroxide therapy	Nonspecific ulcer of scrotum
38 34	F N	Flaccid paralysis of lower extremities; xanthochromic spinal fluid with cell count 500, mostly lymphocytes; Pandy test 4 plus	4/26 4/28	Moderate 2 plus	.....	..	.....	..	8.49 8.01 7.73	....	....	....	....	Neg. ..... Neg.	2 plus ..... Neg.	... ...	.. .. ..	....	4 plus 4 plus 1 plus	2 plus Neg. Neg.	Died; autopsy not obtained	Transverse myelitis; syphilis (?)

blood volume by the dye methods and the computation of total available fluids by the thiocyanate or sucrose methods were too elaborate and time consuming for our work. The McClure-Aldrich intradermal wheal absorption test has not been proved to be a sufficiently sensitive index of the state of hydration. The opinion has been voiced that a patient is not dehydrated when the urinary output is adequate. This concept is not entirely correct, for it is known that in the presence of tubular damage the reabsorption of water is impaired and a large amount of dilute urine may be excreted even when the patient is dehydrated. Moreover, this type of renal damage, by its failure to conserve water and fixed base, may be a factor in the production of dehydration.

The picture is further complicated by the demonstration of Nadal and coworkers [13] that two distinct types of dehydration may occur in human subjects.

TABLE 2.—*Classification of Thirty-Eight Cases of Hyperproteinemia (Summary of Table 1)*

Condition	Number of Cases in Group	Cases of Each Type of Disease	Number of Each Case in Table 1
Hepatic disease	9		
Cirrhosis		6	1, 2, 3, 5, 6 and 7
Cirrhosis with primary carcinoma of liver		1	8
Acute hepatitis		1	4
Catarrhal jaundice		1	9
Lymphogranuloma venereum	6		10, 11, 12, 13, 14
Chronic suppurative infections	4		
Calculous pyelonephritis		1	16
Calculous pyonephrosis		1	17
Pelvic cellulitis		1	18
Moist gangrene of leg with diabetes mellitus		1	19
Acute infections	4		
Scarlet fever		2	20, 21
Erysipelas		1	22
Acute pyelonephritis		1	23
Tuberculosis	2		
Pulmonary, with tuberculous peritonitis		1	24
Pulmonary		1	25
Bacterial endocarditis	2		26, 27
Malaria	1		28
Syphilis (with hepatitis)	1		29
Multiple myeloma	1		30
Boeck's sarcoid	1		31
Extreme dehydration	2		
From vomiting and diarrhea		1	32
From diabetic coma		1	33
Miscellaneous conditions	6		
Generalized adenopathy (cause undiagnosed)		2	34, 35
Alcoholism with mental deterioration		1	36
Nonspecific ulcer of scrotum		1	37
Transverse myelitis (cause unknown)		1	38

They showed that dehydration resulting from simple deprivation of water is characterized by thirst and oliguria, and does not lead to impairment of circulation or to hemoconcentration, whereas dehydration resulting from abnormal loss of salt results mainly in loss of extracellular fluid, reduction of plasma volume, hemoconcentration and disturbances of the circulation.

Thus, it is apparent that objective determination of the state of hydration was impossible in most of our cases. Our interpretation of the state of hydration rested on clinical observations (vomiting, diarrhea, sweating, deprivation of water, thirst, dryness of mucous membranes, loss of turgor of tissue, oliguria) and on judicious evaluations, under the limitations mentioned, of the laboratory data listed under "Dehydration" in table 1.

Another difficulty that arose when we were interpreting our results was the fact that in hyperproteinemic states the blood protein levels may fluctuate daily and

13. Nadal, J. W.; Pedersen, S., and Maddock, W. G.: Comparison Between Dehydration from Salt Loss and from Water Deprivation, J. Clin. Investigation **20**:691-703 (Nov.) 1941.

may even drop to normal at times.[1] Therefore, if a serum sample was obtained at a time when the protein concentration was temporarily normal, a case of hyperproteinemia might have been overlooked. The number of cases thus overlooked was, no doubt, small.

Still another difficulty was the frequency of cases in which multiple pathologic conditions occurred in the same patient. As previously mentioned, when one pathologic condition known to be a frequent cause of hyperproteinemia was found, we assumed that this was the main or only cause in that particular patient.

In general, our findings confirm the observations of other workers.

Hyperglobulinemia occurs in some types of hepatic disease, especially cirrhosis. In the past it was commonly accepted that the change in the blood protein in cirrhosis consisted of diminution of the total protein concentration. Recently, various authors have demonstrated a rise in serum globulin in some cases of hepatic cirrhosis. Published values as a rule revealed sufficient concomitant lowering of the serum albumin to maintain the total protein of a normal or even a lower than normal level, a situation not usually found in other diseases associated with hyperglobulinemia, in which hyperproteinemia usually resulted. Thus Gutman and Wise [14] found globulin values of 6.0, 5.6 and 5.0 Gm. per hundred cubic centimeters with corresponding total protein values of 8.4, 7.4, and 7.2 Gm. in 3 cases of cirrhosis. Peters and Eisenman,[15] in a series of cases, found the globulin above or in the upper range of normal in every case but 1. They stated "in cirrhosis of the liver . . . globulin may rise far above the normal level." They cited other observers who had reported hyperglobulinemia in hepatic cirrhosis, and one who produced it by inducing experimental injury of the liver. Foley, Keeton and others [16] stated "an increase in plasma globulin and a decrease in plasma albumin are associated not infrequently with chronic hepatic disease, particularly with cirrhosis of the liver."

Our series of 9 cases of hepatic disease includes 6 cases of hepatic cirrhosis, 1 of cirrhosis with a superimposed primary carcinoma of the liver, 1 of acute hepatitis in a patient with alcoholism in whom underlying cirrhosis or fatty liver could not be excluded, and 1 case of acute catarrhal jaundice in a young man. It seems, then, that hyperglobulinemia (and hyperproteinemia) may also occur in some cases of acute hepatic disease. In all of these cases the total protein was elevated, ranging between 8.0 and 13.4 Gm. per hundred cubic centimeters. We can give no reason for the occurrence of hyperproteinemia and hyperglobulinemia in some instances of certain types of hepatic disease and not in others.

The common association of hyperproteinemia with lymphogranuloma venereum was demonstrated by the extensive pioneer studies of Gutman and his co-workers.[17] In 26 of the 35 cases they studied the total protein values were above 8.0 Gm.

14. Gutman, A. B., and Wise, C. R.: Positive Formol-Gel Reactions Associated with Hyperglobulinemia in Lymphogranuloma Inguinale, Multiple Myeloma, and Hepatic Cirrhosis, Proc. Soc. Exper. Biol. & Med. **35**:124-128 (Oct.) 1936.

15. Peters, J. P., and Eisenman, A. J.: Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, Am. J. M. Sc. **186**:808-833 (Dec.) 1933.

16. Foley, E. F.; Keeton, R. W.; Kendrick, A. B., and Darling, D.: Alterations of Serum Protein as an Index of Hepatic Failure, Arch. Int. Med. **60**:64-76 (July) 1937.

17. Gutman, A. B., and Gutman, E. B.: Calcium Protein Relation in Hyperproteinemia: Total and Diffusible Calcium in Lymphogranuloma Inguinale and Myeloma, Proc. Soc. Exper. Biol. & Med. **35**:511-515 (Dec.) 1936. Gutman, A. B.; Gutman, E. B.; Jillson, R., and Williams, R. D.: Acid-Base Equivalence of the Blood in Diseases Associated with Hyperglobulinemia with Special Reference to Lymphogranuloma Inguinale and Multiple Myeloma. J. Clin. Investigation **15**:475-484 (Sept.) 1936. Gutman and Wise.[14]

per hundred cubic centimeters, 11.2 Gm. being the highest value reached. The hyperproteinemia in their series was more marked in cases of rectal stricture. Jones and Rome [18] studied 79 patients with lymphogranuloma venereum, the majority of whom had total protein values above 8.0. The mean total protein value was 8.55, and the highest value obtained was 13.33 Gm. per hundred cubic centimeters. Schamberg [19] studied the course of the plasma protein changes in 20 Negroes with early lymphogranuloma venereum treated with sulfanilamide. All of his patients presented initially hyperglobulinemia, the globulin reverting toward the normal level as clinical improvement was manifest. Seventeen of the 20 patients in his series had total protein values above 8.0 Gm. at one time or another during the course of their disease. Jeghers and Selesnick [2] stated that since this disease is now known to be common in this country, it must always be considered when high blood protein is found, and excluded by the Frei test. Conversely, all persons with inguinal adenitis or rectal stricture should have blood protein determinations as part of their diagnostic study. The highest total protein value in our series of 6 cases of lymphogranuloma venereum was 11.44 Gm. per hundred cubic centimeters and the highest globulin value 7.66 Gm.

Hyperglobulinemia and occasionally hyperproteinemia have been reported with various and usually chronic infections. Schamberg [19] stated that "hyperglobulinemia of greater or less extent occurs in most infectious diseases." Bing [20] stated that "the most frequent cause of hyperglobulinemia is an infection, and the increase of serum globulin has been placed in connection with the formation of antibodies, it having been shown that the function of antibodies is associated with the globulins." He stated further that "the hyperglobulinemia that occurs with the ordinary acute infections is only slight in most cases" and "in only rare cases is the increase of globulin so great that one can speak of hyperproteinemia as well . . . on the other hand, in chronic specific or nonspecific infections it is more often the case that hyperglobulinemia is so excessive that it leads to hyperproteinemia."

The cases of acute infection with hyperproteinemia in our series include 2 of scarlet fever, 1 of erysipelas and 1 of acute pyelonephritis.

The cases of chronic infection listed in our series include instance of various types of tuberculosis which have often been reported with hyperproteinemia and hyperglobulinemia. Kurten,[21] using the formaldehyde-gel test as an index of hyperglobulinemia, obtained a positive result in 60 to 80 per cent of cases of subacute bacterial endocarditis. Jeghers and Selesnick suggested that this disease will eventually be included in the group of diseases in which hyperproteinemia is common. Gutman included a case of this disease with high total protein and globulin values. Hyperproteinemia and hyperglobulinemia have been reported in cases of malaria. Chronic suppurative infections are conspicuous as a cause of hyperproteinemia in our series.

It was the opinion of earlier workers that syphilis produces an increase in globulin and total protein. Rowe [22] in 1916 stated that "in syphilis the globulin frac-

18. Jones, C. A., and Rome, H. P.: Serum Proteins, Takata-Ara Reaction, and Liver Function Tests in Lymphogranuloma Venereum, Am. J. Clin. Path. **9**:421-436 (July) 1939.

19. Schamberg, J. L.: Course of the Plasma Protein Changes in Early Lymphopathia Venereum Under Treatment with Sulfanilamide, Am. J. M. Sc. **201**:67-81 (Jan.) 1941.

20. Bing, J.: Further Investigations on Hyperglobulinemia (Occurrence and Degree of Hyperglobulinemia in Various Diseases: Ratio Between Hyperglobulinemia, Hyperproteinemia and Hypoalbulinemia; Formolgel-Reaction), Acta med. Scandinav. **103**:547-564, 1940.

21. Kurten, H.: Zur Diagnose der Endocarditis lenta, Ztschr. f. d. ges. exper. Med. **61**: 494, 1928.

22. Rowe, A. H.: Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med. **18**:455-473 (Oct.) 1916.

tion is definitely increased while the total protein remains about normal." Lloyd and Paul [23] in 1928 wrote "it has of course been known for a long time that the globulins in syphilitic serum are increased." He studied 11 cases of secondary syphilis, all but 3 of which had values for globulin above 3.0 Gm. per hundred cubic centimeters but only 1 of which had a total protein value above 8.0 Gm. Wu [24] reported 2 cases of syphilis with hyperproteinemia. Recently the occurrence of hyperglobulinemia and hyperproteinemia in uncomplicated syphilis has been questioned, and as demonstrated by Jones and Rome,[18] may be due to the concomitant presence of lymphogranuloma venereum. The latter workers did not find marked increase in serum globulin in patients with syphilis except in those who also had a positive Frei test. Unfortunately, the Frei test was not done in our single case of syphilis.

The interpretation of the positive serologic reactions in 8 other cases in this table and the relation of hyperproteinemia to the false serologic reaction for syphilis and the anticomplementary Wassermann reaction constitute the subject of another report.[25]

Salvesen [26] reported 3 cases of Boeck's sarcoid with hyperproteinemia. One case of sarcoid is reported in this work.

Only 1 instance of multiple myeloma occurred in our series. This no doubt merely reflects the rarity of the condition, since hyperproteinemia and hyperglobulinemia occur with great frequency in cases of this disease. Sweigert [27] cited 35 cases of multiple myeloma in which the blood proteins were determined; in 20 the values were over 8.0 Gm. per hundred cubic centimeters. Gutman and Gutman [17] in 1936 cited among 57 published cases of multiple myeloma 35 with hyperproteinemia. Bing [20] added 14 cases of multiple myeloma with hyperglobulinemia. These studies show that hyperproteinemia probably occurs in from 50 to 60 per cent of cases of multiple myeloma. According to Jeghers and Selesnick it is of greater aid in the diagnosis of this condition than Bence Jones proteinuria. The highest total protein values on record (up to 16.0 Gm. per hundred cubic centimeters) have been reported with this disease.

In the miscellaneous group in our series are 2 cases of undiagnosed generalized lymphadenopathy. The clinical pictures in these patients were compatible with infectious mononucleosis in spite of negative heterophilic agglutination tests. One case of transverse myelitis of unknown cause is reported. Permission for an autopsy could not be obtained. In this connection Bing and his collaborators reported 3 cases of a syndrome which apparently had never been published before: "sepsis lenta with considerable involvement of the central nervous system and changes in the spinal fluid."

There were 2 cases in our series in which the hyperproteinemia was clearly due to dehydration alone. One of the patients was a 56 year old Negro woman admitted to the hospital in diabetic coma. The total protein on admission was 9.0 Gm. per

23. Lloyd, R. B., and Paul, S. N.: Protein Graphs in Kala-Azar, Indian J. M. Research **16**:529-535 (Oct.) 1928.

24. Wu, H.: New Colorimetric Method for Determination of Plasma Proteins, J. Biol. Chem. **51**:33-39 (March) 1922.

25. Cardon, L., and Atlas, O. H., with others: Biologic False Positive Reactions for Syphilis Associated with Hyperproteinemia: A Preliminary Report, Arch. Dermat. & Syph. **46**:713-720 (Nov.) 1942.

26. Salvesen, H. A.: Sarcoid of Boeck: Disease of Importance to Internal Medicine, Acta med. Scandinav. **86**:127-151, 1935.

27. Sweigert, C. F.: Multiple Myeloma with Hyperproteinemia, Am. J. M. Sc. **190**:245-256 (Aug.) 1935.

hundred cubic centimeters, of which 6.25 Gm. was albumin and 2.75 Gm. globulin (normal albumin-globulin ratio).

The other patient, a Negro man 50 years of age, gave a history of vomiting, diarrhea and little intake of food or fluid for a period of a week. The initial level of the total serum protein was 13.7 Gm. per hundred cubic centimeters. Five days later, after the patient had been hydrated, the level of the total serum protein returned to 7.0 Gm. per hundred cubic centimeters. Unfortunately, the levels of albumin and globulin were not determined.

Attempts to obtain other similar cases by examining the blood of patients that appeared clinically dehydrated were disappointing in that normal values for total protein were usually obtained even in several other cases of diabetic coma. The reasons for this may be twofold. First, the degree of dehydration necessary to produce hemoconcentration may be more extreme than is commonly thought, and, second, the usual indigent type of patient admitted to the Cook County Hospital frequently suffers from anemia and nutritional hypoproteinemia. However, in 8 of the 38 cases in this study, dehydration as manifested by clinical and laboratory signs was considered to contribute to the hyperproteinemia present.

Special Tests.—(*a*) Takata-Ara Reaction: The extensive and conflicting literature available concerning this recently popularized test was carefully reviewed and evaluated by Magath.[28] It has been generally thought that the test is positive in any case of disease associated with elevation of the serum globulin above 3 Gm. per hundred cubic centimeters and a reversal of the albumin-globulin ratio. Magath, however, cited as many observers who denied this relationship as those who supported it. The conflicting results of various authors cited by Magath may be summarized as follows: (1) "in a high percentage of positive reactions the albumin-globulin ratio is reversed and in even a higher percentage there is some alteration in either the relative or the absolute amounts of these proteins." (2) "In an appreciable number of cases the albumin-globulin ratio is not disturbed when the Takata-Ara reaction is positive." (3) "Increase in the globulin fraction of the serum, both relatively and absolutely, does occur in the majority of cases, but there are many cases in which it does not. Conversely, there are many cases with changes in the globulin without positive Takata reactions." (4) "Many positive reactions are obtained in cases in which the level of serum protein is low and in which the albumin-globulin ratio is not reversed."

A study of the literature reveals that the Takata-Ara reaction is so frequently positive in cases of hyperproteinemia that it has been used as a simple means of detecting hyperproteinemia. Jeghers[29] noted markedly positive Takata-Ara reactions in each of 5 cases of multiple myeloma associated with hyperproteinemia and hyperglobulinemia. Jeghers and Selsnick reported the reaction positive in 9 of 10 cases of hyperproteinemia and hyperglobulinemia in which it was performed. Salvesen[26] reported the reaction positive in his cases of Boeck's sarcoid associated with hyperproteinemia, and it has been reported positive by numbers of workers in cases of lymphogranuloma venereum associated with increased protein concentration. Inasmuch as in hyperproteinemia it is globulin that is usually increased, it is understandable why a strongly positive reaction occurs in this condition.

(*b*) Formaldehyde-Gel Reaction: The formaldehyde-gel reaction (known also as the formal-gel test, the Gate-Papacosta reaction, the Fox-Mackie reaction and

28. Magath, T. B.: Takata-Ara Test in Liver Disease, J. Lab. & Clin. Med. **26**:156-173 (Oct.) 1940.

29. Jeghers, H.: Detection of Hyperproteinemia Due to Multiple Myeloma by Means of Takata-Ara Reaction, J. Lab. & Clin. Med. **22**:425-430 (Jan.) 1937.

Kurten's reaction) has been shown to be positive usually under the same conditions that produce a positive Takata-Ara reaction, and consequently it has been used as a simple method of detecting hyperproteinemia and hyperglobulinemia. The reaction depends on the formation of a gel when 36 per cent neutral solution of formaldehyde is added to blood serum. Bing [30] and others have shown that the reaction is positive whenever the globulin concentration is above 3.5 Gm. per hundred cubic centimeters. Hassan and Salah [30] made a comparative study of the formaldehyde-gel and Takata-Ara reactions in relation to serum proteins. In 85 per cent of 600 serums examined there was similiarity between the results of the two tests. They concluded that a strongly positive formaldehyde-gel reaction is always associated with hyperglobulinemia (usually euglobulinemia) and that such serums contain 4 per cent or more of globulin. The reaction cannot be applied as an absolute quantitative method for determining the degree of hyperglobulinemia but because of its simplicity and reliability can be used routinely to detect the presence of hyperglobulinemia.

Twenty-eight Takata-Ara tests and 30 formaldehyde-gel tests done in 20 of our cases of hyperproteinemia were positive regardless of the clinical condition causing the hyperproteinemia. In only 2 instances was there disagreement between the two tests. Of the 20 instances in which the values for the globulin fraction were available the lowest concentration of globulin to give a positive Takata-Ara or formaldehyde-gel test was 3.5 Gm. per hundred cubic centimeters. These results also substantiate the observations of other workers that the formaldehyde-gel and Takata-Ara reactions are not specific for any particular diseases but are positive in any condition producing an increased concentration of globulin above 3.5 Gm. per hundred cubic centimeters. The correlation of these two tests in conditions of hyperproteinemia shows that they are practically interchangeable, and since the formaldehyde-gel reaction is of greater simplicity, it may be conveniently substituted for the Takata-Ara reaction in detecting hyperglobulinemia.

(*c*) Increased Sedimentation Rate: The exact underlying mechanism of the increased rate of sedimentation of the red blood cells in various pathologic conditions is not as yet known although the literature on the subject is voluminous. Moreover, in spite of these extensive investigations, the present day knowledge of the exact cause of the increased rate is not much greater than the information contained in the pioneer work of Fahraeus.[31] He stated that although there was no correlation between the sedimentation rate and the concentration of total plasma protein, an increased concentration of globulin and of fibrinogen frequently occurred coincidentally with increased sinking velocity. He did not believe, however, that there was a direct relation of cause and effect. Ropes and his associates [32] concluded that there is not a quantitative correlation between the sedimentation rate and the concentration of fibrin, globulin or total protein. It has been frequently observed that hyperproteinemia is almost invariably associated with a markedly increased sedimentation rate even in the absence of fever or infection. In fact, some of the most rapid sedimentation rates on record have been associated with hyperproteinemia. Bendien and Snapper [33] stated that the following empiric

30. Hassan, A., and Salah, M.: Comparative Study of Formol-Gel and Takata-Ara Reactions in Relation to Serum Proteins, J. Trop. Med. **42**:169-174 (June 15) 1939.

31. Fahraeus, R.: Suspension Stability of Blood, Physiol. Rev. **9**:241-274 (April) 1929.

32. Ropes, M. W.; Rossmeisl, E., and Bauer, W.: Relationship Between Erythrocyte Sedimentation Rate and Plasma Proteins, J. Clin. Investigation **18**:791-798 (Nov.) 1939.

33. Bendien, W. M., and Snapper, I.: Zusammenhang zwischen der Senkungsgeschwindigkeit der roten Blutkörperchen und dem Eiweisspektrum, Biochem. Ztschr. **235**:14-34, 1931.

formula expresses the relation of the various factors involved in the sedimentation of the red cells.

$$\text{Sedimentation rate} = \frac{45}{\text{cell volume}} \times [(\text{fibrinogen } \% - 3.5 \times 12 + (\text{globulin } \% - 22 \times 2.5)]$$

It can be seen from this formula that the sedimentation rate increases with the concentration of globulin but that other factors are also operative.

Twenty-six sedimentation rates were determined by the Westergren [34] method in 17 cases of hyperproteinemia in our series, of which 23 were corrected for anemia by the hematocrit (Wintrobe and Buell [35]), according to the method of Plass and Rourke.[36] The mean of the 26 uncorrected sedimentation rates was 150 mm. per hour (the normal does not exceed 20 mm. per hour). Some of the values obtained were among the highest recorded in the literature and were seen even in the absence of fever or infection. The mean of the 23 corrected sedimentation rates was 80 mm. per hour. The lowest corrected rate was 42. No linear correlation could be established between the concentration of total protein, albumin or globulin and the sedimentation rate, but one may conclude that in the presence of true hyperproteinemia the sedimentation rate is invariably increased to a marked degree.

Postmortem examination of 6 hyperproteinemic patients and biopsy of the livers of 2 hyperproteinemic patients failed to reveal any consistent histopathologic changes, such as the proliferation of the reticuloendothelial system suggested by Bing, except in the 2 cases of subacute bacterial endocarditis in which such proliferation was evident and in the case of multiple myeloma in which there was marked hyperplasia of plasma cells.

SUMMARY AND CONCLUSIONS

Fifty-four patients with total serum protein above 8.5 Gm. per hundred cubic centimeters were found by random sampling examination of 4,370 serums, by the falling drop method giving the incidence of hyperproteinemia in the Cook County Hospital as 1.2 per cent.

In the Cook County Hospital hyperproteinemia is most frequently found to be associated with hepatic diseases, lymphogranuloma venereum, certain acute and chronic infections and states of extreme dehydration.

The concentration of total protein is correlated with the concentration of globulin in hyperproteinemic serums.

The results of the Takata-Ara and the formaldehyde-gel test are interchangeable and are almost invariably positive in conditions associated with hyperproteinemia and hyperglobulinemia.

The sedimentation rate is regularly increased to extreme degrees in hyperproteinemic conditions, but no linear correlation exists between the concentration of total protein or globulin and the rate of sedimentation.

No consistent correlation between particular histopathologic changes and hyperproteinemia could be demonstrated in this series of cases.

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BLOOD FLOW IN EXTREMITIES AFFECTED BY ANTERIOR POLIOMYELITIS

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It has generally been accepted that an extremity affected by anterior poliomyelitis, with atrophy of voluntary muscle, suffers from a definite diminution in blood supply. In fact, the rationale for some of the methods of treatment of this condition has had for a purpose the augmentation of the peripheral circulation through the involved muscles. Examination of literature, however, reveals that definite proof for such a view does not exist. In order to elucidate this point, the peripheral circulation in a series of 27 patients with anterior poliomyelitis was studied by means of the venous occlusion plethysmographic method.

METHOD

The series was limited to subjects with unilateral involvement of an extremity, so that in each instance the contralateral normal limb could be utilized as a control. Readings of blood flow during rest, in cubic centimeters of blood per minute per hundred cubic centimeters of limb volume, were obtained either on two forearms or on two legs at a bath temperature of 32 C. (temperature of the water in the plethysmograph) and a room temperature of 25 to 27 C., according to a technic previously described.[1] In the majority of subjects the response to a five minute period of local anoxia was also studied. This was measured by applying an arterial occlusion pressure to the extremity, proximal to its insertion in the plethysmograph, and then after release of the pressure determining blood flow every ten seconds during the subsequent state of reactive hyperemia.[2] From the readings obtained a graph was constructed, and by means of a planimeter the amount of excess blood flow, the quantity over and above that which would have ordinarily entered the extremity, was determined.[2] This figure was expressed as the quantity of excess blood per hundred cubic centimeters of limb volume elicited by each minute of arterial occlusion.

In most instances readings of cutaneous temperature were obtained repeatedly over a period of six hours by means of a Tycos dermatherm. During this time the subjects remained indoors.

RESULTS

Of the 27 subjects in the series, 5 were tested within two to four weeks after the termination of the contagious stage of the disease. At this time atrophy of muscles was generally not significant, although definite weakness or paralysis of the extremities was present. In the remaining 22 subjects, the attack of polio-

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myelitis had taken place from one to thirty years previously and marked involvement of muscle existed in most instances. There was no apparent difference in the rates of blood flow observed in the two groups (table 1), and hence the results will be discussed collectively.

TABLE 1.—*Blood Flow During Rest in an Extremity Affected by Anterior Poliomyelitis as Compared with That in the Contralateral Normal Limb* *

Subject No.	Blood Flow, Cc./Min./100 Cc. of Limb Volume: Normal Limb	Abnormal Limb	Comment	Subject No.	Blood Flow, Cc./Min./100 Cc. of Limb Volume: Normal Limb	Abnormal Limb	Comment
			Forearm				
1	2.5 2.2	5.5 5.2	Acute stage past	4	3.0 3.1 3.2	2.5 3.3 3.1	Chronic; definite atrophy
2	1.4	3.0	Acute stage past	5	3.2 2.9 3.5	2.6 2.6 2.8	Chronic; definite atrophy
3	3.0 3.2	3.0 3.8	Chronic; definite atrophy	6	3.7 4.2 3.9	1.3 1.7 1.5	Chronic; definite atrophy
			Leg				
7	2.1 2.1	2.0 2.2	Acute stage past	18	2.0 2.6 3.0	2.6 2.2 2.9	Chronic; definite atrophy
8	5.8 4.8	5.3 4.9	Acute stage past	19	2.4 2.4 2.9	3.4 3.1 3.1	Chronic; definite atrophy
9	4.5 3.9	6.7 4.1	Acute stage past	20	1.7 1.7	1.3 1.3	Chronic; little atrophy
10	4.1 4.0 4.1	4.6 4.7 5.5	Chronic; definite atrophy	21	1.2	0.8	Chronic; some atrophy
11	5.1 5.3	3.8 6.3	Chronic; definite atrophy	22	2.9 3.1 3.0	1.4 2.4 2.4	Chronic; definite atrophy
12	5.1 5.3	6.2 7.4 6.3	Chronic; definite atrophy	23	3.6 3.2 3.5	2.7 3.5 2.9	Chronic; definite atrophy
13	3.6 3.1	3.6 3.7 5.5	Chronic; definite atrophy	24	3.7 3.6 4.2	0.9 1.5 2.1	Chronic; definite atrophy
14	3.9 3.8 4.6	4.8 5.0	Chronic; definite atrophy	25	4.0 3.8 3.6	2.0 2.4 2.2	Chronic; definite atrophy
15	1.7	2.4	Chronic; definite atrophy	26	1.3 1.4	0.7 0.8	Chronic; definite atrophy
16	2.3 2.0 1.2	1.9 2.4 1.9	Chronic; definite atrophy	27	7.0 5.0 6.9 6.5	2.2 4.2 5.2 6.2	Chronic; definite atrophy
17	1.9 1.6 2.0	1.2 1.6 1.8	Chronic; definite atrophy				

* Each reading represents the average of ten determinations. In most of the subjects at least three sets of readings were made during the experimental period, at half hour intervals. These are presented in the table in the order they were obtained.

When the readings obtained at the beginning of the experimental period were examined, it was found that in 14 instances the average blood flow in the involved extremity was either the same as or definitely greater than that in the control contralateral limb (table 1). The readings for the affected limb in the remaining 13 subjects were either somewhat or definitely reduced. However, on making further determinations over the next hour or two, an increase in the rate of blood flow in the paralyzed extremities was observed in the latter subjects. In fact, in 9 of them the second set of readings now yielded values which were either only slightly

less than, the same as or greater than those for the control side (table 1). In only 4 of the paralyzed extremities did the blood flow continue to be significantly decreased.

In respect to the response to a period of arterial occlusion, examination of table 2 reveals that in 9 of 23 subjects the blood flow repayment was the same in the involved and in the normal extremity. In 6 subjects it was slightly decreased, and in 3, slightly increased. In only 5 was there any significant difference in the reaction of the blood vessels in the limb affected by poliomyelitis as compared with that on the control side; in 3 the response was greater than normal, and in 2 it was less than normal.

In the case of determinations of cutaneous temperature the first set uniformly showed a significant decrease on the paralyzed side, in some instances to the extent

TABLE 2.—*Response to a Five Minute Period of Arterial Occlusion in an Extremity Affected by Poliomyelitis as Compared with That in the Contralateral Normal Side*

	Normal Limb			Involved Limb			
Subject No.	Resting Flow *	Repayment †	Maximum Single Reading ‡	Resting Flow *	Repayment †	Maximum Single Reading ‡	Comment
			Forearm				
1	2.2	2.1	13.0	5.2	3.3	11.4	Acute stage past
3	3.1	1.0	9.1	3.4	3.4	17.6	Chronic
5	3.2	2.8	18.9	2.9	2.6	6.3	Chronic
4	3.3	2.5	15.2	3.0	2.2	10.6	Chronic
6	4.1	3.1	18.1	1.8	1.2	9.7	Chronic
			Leg				
8	4.9	3.6	21.1	5.2	1.4	13.5	Acute stage past
7	2.1	2.4	12.1	2.0	2.5	19.4	Acute stage past
26	1.4	0.7	5.9	0.7	0.4	5.6	Chronic
16	1.9	0.7	7.0	2.3	0.6	6.7	Chronic
14	4.2	2.0	14.8	4.9	2.6	17.7	Chronic
11	5.2	1.4	14.3	5.1	1.4	10.1	Chronic
13	3.3	3.6	15.4	4.6	2.4	15.5	Chronic
18	2.8	0.9	9.2	1.9	1.9	10.4	Chronic
12	5.2	1.6	13.9	6.4	0.9	11.2	Chronic
17	1.8	1.8	7.8	1.6	1.3	10.1	Chronic
22	3.0	1.9	16.5	2.0	1.6	9.2	Chronic
20	2.0	1.6	5.5	1.4	1.2	6.9	Chronic
10	4.1	1.4	10.9	5.1	1.8	13.4	Chronic
23	3.4	2.5	15.6	3.2	2.5	12.2	Chronic
27	6.7	1.1	13.5	4.6	1.1	9.1	Chronic
19	2.7	1.7	6.9	2.8	1.9	15.0	Chronic
24	4.0	1.0	8.7	1.2	1.4	6.2	Chronic
25	4.0	1.6	9.3	2.3	1.6	15.7	Chronic

* The blood flow was read in cubic centimeters per minute per hundred cubic centimeters of limb volume.

† Repayment was calculated as the amount of excess blood per hundred cubic centimeters of limb volume entering an extremity in a period of reactive hyperemia for each minute of arterial occlusion.

‡ The maximum single reading represented the highest rate of blood flow obtained during a period of reactive hyperemia.

of 5 C. (table 3). However, with the second and the third set, taken three and six hours, respectively, after the first one, the difference between the normal and the abnormal limb definitely diminished, with the result that in many subjects the readings for both limbs were the same by the time the six hour experimental period was terminated (table 3).

COMMENT

When determinations of blood flow are made on a series of normal subjects with the venous occlusion plethysmographic method, it is assumed that the relative amounts of skin, muscle, fat and bone in the limb are fairly constant in every instance. Since the blood flow through bone is not measured with this procedure, it is generally accepted that the reading, although expressed as the number of cubic centimeters of blood per minute per hundred cubic centimeters of total limb volume, actually represents the composite rate of circulation through skin and muscle

only. In the case of an atrophied extremity, the question arises whether the normal proportion of skin, muscle and bone is disturbed and, further, if it is, whether a figure indicating the rate of blood flow per hundred cubic centimeters of limb volume in this type of limb can be compared with a similar reading for a normal limb.

TABLE 3.—*Changes in Cutaneous Temperature in an Extremity Affected by Anterior Poliomyelitis and in the Contralateral Normal Extremity*

	Upper Extremity				
		Forearm			
Subject No.	Arm, Lower Third	Upper Third	Middle Third	Lower Third	Hand, Dorsum
3	−0.5	−0.1	−0.5	−1.0	−0.7
	−0.3	−0.1	−0.4	−0.5	−0.3
	+0.5	+0.3	−0.5	±0.0	+0.2
6	−2.0	−1.3	−1.3	−1.6	−0.3
	−1.5	−0.9	−0.9	−0.6	−0.4
	−1.2	−1.3	−1.5	−1.2	−0.5
5	−1.6	−0.6	−0.7	−0.1	−1.1
	−0.7	−0.4	−1.2	−0.1	−0.1
	−0.1	−0.5	±0.0	−0.3	±0.0
4	−1.3	−0.7	−0.6	−0.6	−0.4
	−1.0	−0.6	−0.5	−0.1	−0.1
	+0.3	−0.7	−0.3	−0.3	−0.1
	Lower Extremity				
		Leg			
Subject No.	Thigh, Lower Third	Upper Third	Middle Third	Lower Third	Foot, Dorsum
23	−0.8	−1.6	−4.2	−3.9	−4.2
	−0.6	−1.0	−3.9	−4.3	−4.0
	−0.3	−0.5	−1.9	−1.7	−2.2
27	−0.5	−0.5	−2.4	−1.5	−1.1
	−0.5	−0.4	−1.7	−1.2	−0.6
	−0.2	−0.6	−2.3	−2.3	−2.5
12	−1.2	−1.1	−0.5	−2.9	−3.0
	±0.0	−0.3	−0.4	−2.9	−3.8
	−0.5	−0.4	−0.3	−0.2	±0.0
13	−1.8	−1.8	−2.2	−1.9	−2.1
	−0.4	−1.1	−1.4	−1.1	−1.2
	+0.2	−0.7	−0.7	−0.1	−0.2
22	+0.2	−2.4	−2.9	−2.9	−2.5
	−0.6	−1.9	−0.9	−0.5	−1.4
20	+0.3	−0.1	−0.8	−1.7	−0.7
	−0.3	−0.2	−1.2	−1.4	−0.7
	−0.5	+0.1	−0.1	−0.4	−0.7
18	−1.4	−2.6	−3.6	−2.3	−3.7
	−1.3	−2.0	−2.6	−1.6	−0.9
	−0.9	−0.6	−2.6	−2.4	−3.3
17	−0.9	−1.4	−2.5	−3.6	−3.8
	−0.4	−1.9	−2.6	−3.6	−4.3
19	−0.2	−2.0	−2.9	−2.1	+0.1
	−0.1	−0.1	−0.7	−0.4	−1.0
	−0.1	−1.2	−0.3	+0.1	−0.1
24	−2.4	−3.3	−3.3	−2.9	−3.1
	−0.9	−0.4	−1.4	−1.0	−0.9
	−0.1	−0.3	−1.1	−0.6	±0.0
10	−2.2	−3.2	−3.9	−5.3	−5.4
	−0.6	−1.2	−3.0	−2.8	−3.7
14	−1.6	−1.0	−1.3	−1.1	−2.4
	−0.5	±0.0	−1.4	−0.8	−0.6
	−0.3	−0.1	−0.2	−0.3	−0.4

* The readings are set down in the order obtained, i. e., at the beginning, in the middle and at the end of the six hour experimental period. Each figure represents the difference between the cutaneous temperature of the normal extremity and that of the abnormal extremity, the minus sign indicating that the temperature is greater on the normal side and the plus sign indicating that it is greater on the involved side.

In order to elucidate this problem in respect to poliomyelitis, roentgenograms were taken of the normal and the paralyzed limbs of a number of subjects on the same plate and with a single exposure. In all instances it was found that although a definite decrease in the volume of all the tissues existed, the greatest loss occurred

in the quantity of muscle mass. In other words, the bone and, to a lesser degree, the skin now contributed a relatively greater than normal share of the total volume of the atrophied extremity. In view of the fact that the blood flow through bone is not measured by the plethysmographic method, it would seem that measurements of blood flow obtained in an atrophied extremity should be corrected for this factor. If it were possible to do this, it would tend to increase, and certainly not decrease, the magnitude of the readings of blood flow obtained in this type of a limb. In the light of this, our readings for extremities affected by poliomyelitis assume definite significance, since with the exception of a few instances there was no difference observed between the rate of blood flow in the involved extremity, as compared with that in the control limb. Correction of these readings of blood flow would certainly not detract from the validity of this observation.

The occurrence of an initial low cutaneous temperature supports the clinical impression that an extremity affected by poliomyelitis is colder to touch than the contralateral normal limb; these data imply that the cutaneous circulation is reduced in this condition. In accord with this are the reports of a number of investigators [3] who have found that an excessive amount of spasm exists in the peripheral vessels in anterior poliomyelitis. In fact, sympathectomy has been advocated for the relief of this symptom.[3a] The rise in cutaneous temperature that took place over a period of six hours, however, does not completely support such a point of view. The first set of readings of cutaneous temperature was obtained only a short time after the subjects had come in from the outside (all the tests having been performed during the winter months), while the subsequent determinations were made after the skin had been exposed to the environment of a warm room for three to six hours. The rise in cutaneous temperature of the paralyzed extremity can probably be attributed to this circumstance, thus implying that there is no continuous spasm of the cutaneous blood vessels in the affected limb, but only that these vessels respond more markedly to the stimulus of cold than do those of the normal side. Under physiologic conditions, with an optimal environmental temperature, there is no difference in the cutaneous circulation of the two extremities, provided sufficient time has elapsed for the disappearance of the vasoconstriction produced in the cutaneous vessels of the paralyzed limb by cold.

These changes in cutaneous temperature can help to explain the low initial readings of blood flow obtained in the affected extremity in some of our subjects. Since, as previously stated, a composite flow through both skin and muscle is obtained with the plethysmographic method, at the beginning of the experimental period the readings probably represented the portion contributed by the muscle alone, the cutaneous circulation being minimal because of the existing vasospasm. Later, as this was removed and the flow through skin reached a normal level, the total blood flow likewise rose, until it was equal in magnitude to that of the control extremity.

The finding that the circulatory response to a period of arterial occlusion was approximately the same in both the atrophied and the normal extremity appears to have definite significance in relation to the metabolism of the various tissues in the limb. The rationale for such a procedure is based on the assumption that during the period that an artery is occluded by pressure the tissues affected are incurring a blood flow debt, since metabolic processes still continue. On removal of the

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pressure, a period of reactive hyperemia ensues, during which state the blood flow debt is repaid through an increased quantity of blood entering the extremity per unit of time. Hence, the magnitude of this repayment would be a reflection of the requirements of the tissues regarding blood flow. Our data, therefore, are in accord with the view that the metabolism of muscles atrophied by poliomyelitis is no different from that of normal muscles.

SUMMARY AND CONCLUSION

The rate of blood flow during rest was measured by the venous occlusion plethysmographic method in a series of 27 subjects with acute or chronic anterior poliomyelitis of one extremity.

It was found that in the majority of cases the peripheral circulation in the paralyzed limb was the same as that in the contralateral normal extremity; in fact, in some instances it was even significantly greater.

Evidence was obtained which indicated that the cutaneous blood vessels in the extremity affected by anterior poliomyelitis respond more markedly to the stimulus of cold than do those of the contralateral normal limb. The response takes the form of excessive vasoconstriction on exposure to a low environmental temperature and is apparent as a significant decrease in cutaneous temperature.

By studying the changes in blood flow during the reactive hyperemia elicited by a period of arterial occlusion, some evidence was obtained which suggested that the metabolism of muscles atrophied by poliomyelitis is the same as that of normal tissues.

In view of the lack of evidence for the hypothesis that in persons with anterior poliomyelitis the peripheral circulation is reduced, it is concluded that those treatments which have for an aim the increase in blood flow through the affected parts should be critically reexamined for their therapeutic value.

Miss M. Meador, principal, and Mrs. D. Wartman, Miss E. G. Fiefield and Miss R. Pratt, of the Department of Physiotherapy of the Randall J. Condon School, cooperated in this study.

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SERUM CHOLESTEROL LEVEL IN CORONARY ARTERIOSCLEROSIS

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Previous studies [1] have demonstrated an apparent constancy of the serum cholesterol level in normal persons during long periods of observation. It is therefore considered of interest to determine whether or not the serum cholesterol level in patients with coronary arteriosclerosis behaves in a similar manner.

The literature on this subject is not conclusive, and it is based on single determinations of the blood cholesterol in varying numbers of subjects, arbitrarily designated as arteriosclerotic persons and normal controls. From a study of 13 patients with arteriosclerosis and 9 normal persons, Bachmeister and Henes,[2] in 1913, concluded that patients with arteriosclerosis in the stage of development showed an increase in blood cholesterol. In the same year Weltmann [3] reported that 11 of 12 persons with arteriosclerosis had increased blood cholesterol. Denis,[4] in 1917, found that 5 of 14 patients with arteriosclerosis had values for blood cholesterol that exceeded those of 20 control persons. Gorham and Meyers [5] reported in that year that the range of cholesterol levels in 10 patients with arteriosclerosis exceeded that in 14 normal persons. In a well controlled experiment, Mjassnikow [6] stated that 16 patients, 14 of whom suffered from angina pectoris, had elevations in serum cholesterol, the values ranging from 190 to 440 mg. per hundred cubic centimeters. Twenty-five control persons' serum cholesterol amounted to from 120 to 170 mg. per hundred cubic centimeters.

Stepp [7] and Andes, Kampmeier and Adams [8] failed to substantiate the foregoing results. The latter investigators in determining whether or not arteriosclerosis was present in a group of Negroes used as criteria the condition of the radial and dorsalis pedis arteries. (Stiffness of these arteries is now considered evidence

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favoring a diagnosis of medial sclerosis [Mönckeberg's].) Page, Kirk and Van Slyke [9] and Elliot and Nuzum,[10] in studies designed to determine whether or not the serum cholesterol in patients with essential hypertension was elevated, stated that the presence or absence of arteriosclerosis did not seem to influence the cholesterol level. However, in the first of these papers the criteria for the presence of arteriosclerosis were not elaborated on. In the second paper the statement was made that in 18 of 53 patients with hypertension arteriosclerosis of moderate to marked degree as measured by palpation of the peripheral arteries and by ophthalmic examination was present. The blood cholesterol level was not significantly elevated.

The most comprehensive study of this problem is that of Davis, Stern and Lesnich,[11] published in 1937. These authors in a study of the blood lipids and cholesterol in 59 patients with angina pectoris and in 54 controls, found that there was considerable overlapping of the serum cholesterol values in the two groups, but that a small number (20 per cent) with angina pectoris showed values well above the highest normal value.

The present paper records consecutive observations on the serum cholesterol in 15 patients with coronary arteriosclerosis and in 15 relatively normal persons similar with regard to age, all of whom were closely followed over periods up to two years.

METHODS

The group of patients with coronary arteriosclerosis consisted of 15 persons, 13 of whom had electrocardiographic evidence of proved coronary occlusion, whereas the remaining 2 had angina pectoris. The latter 2 patients had positive anoxemia tests [12] for coronary insufficiency. The patients with coronary occlusion were not included in this series until six weeks after the time of the coronary occlusion. Moderate hypertension was present in 2 of these patients.

The control subjects consisted of 7 patients who had recovered six months previously from pneumococcic pneumonia and who had no apparent disease at the time of this study. The remaining 8 persons in the control group had various diseases which were in a stationary (inactive) phase. These were peptic ulcer, tabes dorsalis, rheumatic heart disease, thrombosis of the inferior vena cava and controlled diabetes mellitus. The serum cholesterol of each person was determined by the method of Bloor, Pelkan and Allen [13] twice weekly, then weekly and finally at bimonthly intervals during the period of observation. The basal metabolism of each subject was determined by the Benedict-Roth method. The urine was examined for glycosuria and the blood sugar during fasting was determined, for each person, at frequent intervals.

RESULTS

Table 1 shows the range of values for serum cholesterol in each patient with coronary arteriosclerosis. The number of months of observation, the number of cholesterol determinations, the average cholesterol value with the maximum deviation, and the standard deviation for each of the patients also are tabulated. The periods of observation for the patients with coronary arteriosclerosis varied from two to twenty-six months, and averaged thirteen months for the group. The number of serum cholesterol determinations totaled 742, and the number per patient varied from 8 to 74, averaging 38 for the group. The patient with

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13. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**:191, 1922.

the lowest serum cholesterol had values ranging from 236 to 409 mg. per hundred cubic centimeters, while the one with the highest had values varying between 455 and 550 mg. per hundred cubic centimeters.

The average serum cholesterol values for the individual patients varied from 296 to 499 mg. per hundred cubic centimeters and the mean of the averages for the group was 355 mg. per hundred cubic centimeters. The standard deviations for the individual patients varied from 15.8 to 38.8, the average standard deviation for the group being 24.8.

TABLE 1.—*Variation of the Serum Cholesterol Level in Fifteen Patients with Coronary Arteriosclerosis*

Patient	Age	Sex	Months of Observation	Cholesterol Determinations	Value, Mg. per 100 Cc. Range	Average *	Standard Deviation
1. M. C.	64	F	22	41	333-462	389 ± 73	27.5
2. T. D.†	46	M	26	74	236-409	319 ± 90	36.2
3. L. I.†	43	M	25	69	337-419	377 ± 42	20.0
4. Y. H.	61	F	20	50	265-360	308 ± 52	24.4
5. N. O.	47	M	20	30	292-417	343 ± 63	38.8
6. P. K.†#	42	M	8	25	250-329	296 ± 46	19.4
7. A. G.	48	M	15	59	264-357	312 ± 48	21.9
8. T. J.†	66	M	12	25	309-331	320 ± 32	15.8
9. J. M.	61	M	6	29	248-333	285 ± 48	22.3
10. E. O.	52	M	12	71	286-411	352 ± 66	31.1
11. L. R.†#	47	M	2	8	417-508	471 ± 55	28.3
12. H. G.#	55	M	8	52	352-446	401 ± 49	19.0
13. E. R.#	72	F	9	30	290-373	318 ± 55	25.4
14. R. B.†#	47	F	6	13	325-409	360 ± 40	22.4
15. L. E.#	72	M	6	12	455-550	499 ± 51	19.5
			Av. 13	Total 572 Av. 38		Mean Av. 355	Av. 24.8

* The average is given with the maximum deviation from the mean.
† Dextrose tolerance was normal.
# The values for serum proteins were normal.

TABLE 2.—*Variation of the Serum Cholesterol Level in a Control Group of Fifteen Persons*

Patient	Age	Sex	Months of Observation	Cholesterol Determinations	Value, Mg. per 100 Cc. Range	Average *	Standard Deviation
1. D. C.	22	M	18	30	220-249	234 ± 15	6.9
2. B. S.	35	M	9	20	265-285	273 ± 12	4.7
3. T. R.	72	M	18	37	216-238	222 ± 10	5.7
4. A. P.	73	F	18	32	315-355	334 ± 19	11.6
5. J. N.	54	M	18	33	286-336	308 ± 28	17.5
6. H. F.	42	F	20	38	211-301	278 ± 23	14.5
7. F. K.	64	M	24	40	230-280	256 ± 26	13.8
8. C. P.	28	F	10	9	218-235	224 ± 11	6.3
9. J. O.	47	M	24	42	244-296	268 ± 24	13.7
10. D. C.	15	F	13	10	200-238	214 ± 24	10.3
11. J. S.	34	M	4	8	228-248	240 ± 13	7.1
12. L. J.	38	F	5	21	273-294	283 ± 10	6.7
13. A. N.	52	M	3	7	227-239	231 ± 8	3.2
14. C. R.	50	M	4	8	220-236	226 ± 10	4.6
15. M. G.	35	M	4	7	225-236	232 ± 7	4.3
			Av. 12.6	Total 342 Av. 22.6		Mean Av. 255	Av. 8.7

* The average is given with the maximum deviation from the mean.

These results may be compared with those in table 2, which shows the data for the control group. The average period of observation for the control group was twelve and six-tenths months, and the average number of cholesterol determinations for each person was 22.6, a total of 342 serum cholesterol determinations. The range of serum cholesterol levels in the control persons varied from 216 to 238 mg. per hundred cubic centimeters to 315 to 355 mg. per hundred cubic centimeters. The average serum cholesterol of the subjects lay between 214 and 334 mg.

per hundred cubic centimeters. The mean of the average serum cholesterol determinations for the control group was 255 mg. per hundred cubic centimeters. The standard deviation for the control patients varied from 3.2 to 17.5, and the average standard deviation for the group was 8.7.

From these two tables it can be seen that serum cholesterol was generally higher in the patients with coronary arteriosclerosis than in the control group. Charts 1 and 2 graphically demonstrate the differences between the serum cholesterol values of the two groups. Statistical analysis of these results shows a significant difference between the values of serum cholesterol for the patients with arteriosclerosis and the values for the control group (tables 1 and 2). According to this analysis, there is less than 1 chance in 1,000 that the numerical differences between the two groups could have been obtained by chance.

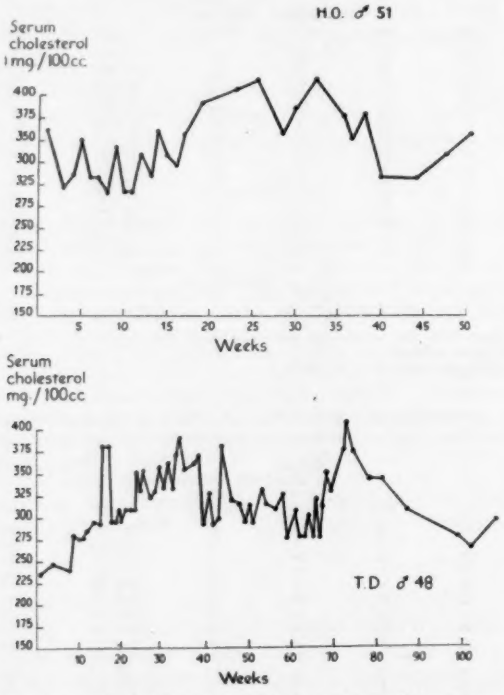

Chart 1.—Variation in serum cholesterol level in 2 patients with coronary arteriosclerosis.

From tables 1 and 2 it is also seen that the fluctuation of the serum cholesterol level of patients with coronary arteriosclerosis is greater than that of the control group. The standard deviation, which is a measure of this fluctuation from the mean, varied from 15.8 to 38.8 in the group with coronary arteriosclerosis and from 3.2 to 17.5 in the control series. The average standard deviation for the former group was 24.8, in contrast to 8.7 for the control group. The ratio of the standard deviation of the group with coronary arteriosclerosis to that of the control group is thus 24.8/8.7 — 2.8. It may be shown that the probability of this ratio occurring by chance is only 0.02 (1 chance in 50). Charts 1 and 2 illustrate this excessive fluctuation in 2 patients with coronary arteriosclerosis in contrast with the relatively constant values in 2 persons of the control group.

Although statistically the aforementioned results are significant, it was felt desirable to make observations on a larger number of patients. For this reason a single determination of serum cholesterol was made on each of 15 additional consecutive patients, aged 40 through 66 years, who were found to have had coronary thrombosis in the absence of diabetes mellitus. Single determinations of serum cholesterol were made on 30 additional normal persons aged 28 through

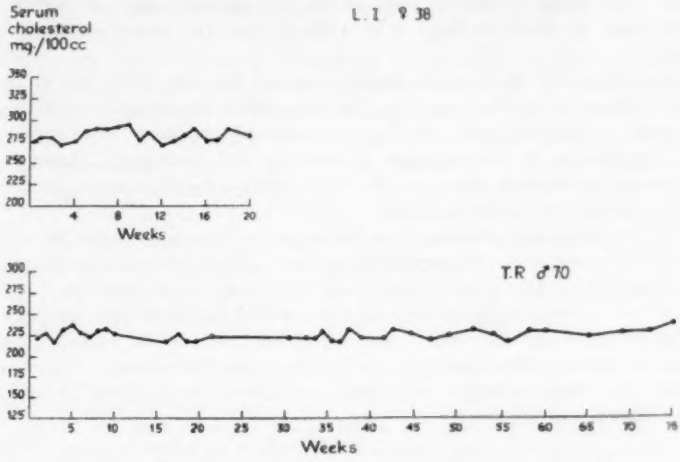

Chart 2.—Variation in serum cholesterol level in 2 controls.

TABLE 3.—*Comparison of the Serum Cholesterol Levels in Fifteen Additional Patients with Coronary Arteriosclerosis and in Thirty Normal Subjects*

Serum Cholesterol, Mg. per 100 Cc., in Patients with Coronary Arteriosclerosis		Serum Cholesterol, Mg. per 100 Cc., in Normal Subjects			
1	264	1	176	16	229
2	279	2	178	17	248
3	294	3	185	18	250
4	297	4	185	19	250
5	305	5	193	20	252
6	312	6	208	21	302
7	315	7	212	22	252
8	315	8	213	23	259
9	335	9	215	24	263
10	335	10	216	25	264
11	342	11	216	26	270
12	355	12	216	27	278
13	369	13	217	28	292
14	380	14	218	29	314
15	505	15	230	30	337
Average 336		Average 236			

65 years. In the second group of patients with coronary thrombosis the serum cholesterol values varied from 264 to 505 mg. and averaged 336 mg. per hundred cubic centimeters (table 3). The range of serum cholesterol in the normal persons varied from 176 to 337 mg. per hundred cubic centimeters and averaged 236 mg. The results confirm the previous observations.

COMMENT

The data presented indicate that the serum cholesterol level in patients with coronary arteriosclerosis is significantly higher than that in a group of control

subjects and also that the cholesterol level in the former group fluctuates widely in contrast with the relative constancy of the level in the control group. Since other disease states may be associated with an elevated level of serum cholesterol (such as uncontrolled diabetes mellitus, chronic glomerulonephritis, nephrosis and myxedema), certain tests were made in order to rule out the possible presence of these conditions. Sugar tolerance tests on 6 patients (table 1) indicated absence of diabetes. Likewise in 6 patients serum proteins showed no abnormalities (table 1). The basal metabolic rates of the 15 patients also fell within normal limits. In view of these findings it is unlikely that the aforementioned diseases were present.

The significance of the present findings cannot be fully evaluated at this time. However, it may be pointed out that the association of elevation and fluctuation of the serum cholesterol level has been considered by many observers to be of etiologic significance in the frequent, premature and widespread development of arteriosclerosis in patients with uncontrolled diabetes mellitus, myxedema, chronic glomerulonephritis and xanthomatosis.

Marked variation and graduation in the extent and the age of cholesterol deposits (atheromas) in arteries is a frequent observation. The process of deposition appears to be discontinuous. It is possible that these variations in the deposits of cholesterol are related to corresponding periods of abnormal fluctuation and elevation of the serum cholesterol level. Coronary arteriosclerosis can now be added to the list of conditions frequently associated with increased serum cholesterol. The mechanism responsible for these changes in serum cholesterol in patients with coronary arteriosclerosis is not apparent.

SUMMARY

The serum cholesterol levels of 15 patients with coronary arteriosclerosis and of 15 controls were determined at frequent intervals for periods up to two years.

The average serum cholesterol values for individual patients with coronary arteriosclerosis varied from 308 to 499 mg. per hundred cubic centimeters, with a mean average of 355 mg. The average serum cholesterol values for the controls varied from 214 to 334 mg. per hundred cubic centimeters, with a mean average of 255 mg. This difference between the two groups was found to be statistically significant.

The fluctuation of the serum cholesterol level in the group with coronary arteriosclerosis as measured by the standard deviation varied from 15.8 to 38.8 and averaged 24.8. The fluctuation of the serum cholesterol level of the control group varied from 3.2 to 17.5, with an average of 8.7. The ratio of 2.8 between the average standard deviations was found to have statistical significance.

Single determinations of serum cholesterol in 15 additional patients with coronary arteriosclerosis and in 30 additional controls present data confirmatory of the long term study.

CONCLUSIONS

1. The serum cholesterol level in patients with coronary arteriosclerosis is significantly higher than the serum cholesterol level in normal subjects.

2. The serum cholesterol level in patients with coronary arteriosclerosis is inconstant and fluctuates widely.

3. The claim of relative constancy of the serum cholesterol level in normal persons is further substantiated.

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MULTIPLE BILATERAL PULMONARY ADENOMATOSIS IN MAN

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A pulmonary lesion of sheep, apparently of infectious origin but resembling a tumor in its morphologic characteristics, has been known since about 1891.[1] It has received such varying names as jagziekte, epizootic adenomatosis, pulmonary adenomatosis and infectious adenomatosis. Very similar and probably identical conditions have been reported under the titles of verminous pneumonia and Montana progressive pneumonia of sheep. A considerable incidence has been found in areas as widely separated as South Africa, Saxony, England, Iceland and Montana. Similar changes have been seen in horses[3] and guinea pigs,[4] and as early as 1903 Löhlein[5] found a picture resembling it in a 69 year old woman. Since that time, the veterinary literature on the subject has become voluminous, and there have been several other human cases recorded.

REPORT OF A CASE

A white man aged 42 was admitted to the Wisconsin General Hospital April 19, 1941, with a cough of two years' duration. The cough had been dry originally, but for a year he had raised about 1 cupful of frothy watery sputum daily. There was never any hemoptysis, but some pain in the upper anterior part of the chest was associated with the cough. For some months he had noticed gradually increasing weakness, a profuse nasal discharge, frequent cold sweats, a low grade fever in the afternoon, shortness of breath on even such slight exertion as talking, decreasing appetite, belching, "gas pains" and progressive loss of weight amounting to 40 pounds (18 Kg.) by the time of admission.

He was a railroad machinist, and he had had no known contact with sheep, nor had he traveled extensively in sheep-raising areas so far as his family knew. Past illnesses included only the usual children's diseases and a rather vague rheumatic episode which had involved a number of joints, with transient local pain and swelling, during the spring of 1940, almost a year after the onset of his present illness. There had been no known infection of the respiratory tract preceding the present illness except for very occasional acute coryza. The family history included no pulmonary diseases so far as he knew, nor had there been known contact with any otherwise.

He was a pale, emaciated (height, 65 inches [165 cm.]; weight, 88 pounds [40 Kg.]), febrile, sick-appearing person, who seemed quite weak and coughed frequently, raising copious amounts of clear watery whitish sputum. The fingers and toes were markedly clubbed, and there was moderate cyanosis of the nails and the mucosae. There was a mucopurulent nasal discharge with some mucosal swelling and injection. The cardiac findings were normal except for tachycardia (rate 100 to 130). The blood pressure was 100 systolic and 70 diastolic.

From the department of pathology of the University of Wisconsin and the Department of Medicine of the State of Wisconsin General Hospital.

1. Eber, A.: Bericht über das Veterinärwesen im Königreich Sachsen für das Jahr 1891, p. 43; cited by Pallaske.[2]

2. Pallaske, G.: Zur Kenntnis der sogennanten Adenomatose oder der multiplen Adenome d'un corynebacille diphtéroïde, Bull. Assoc. franç. p. l'étude du cancer **15**:212-237, 1926.

3. Theiler, A.: Jaagsiekte in Horses, in Seventh and Eighth Reports of the Director of Veterinary Research, Union of South Africa, April 1918, p. 59.

4. Grumbach, A.: Tumeurs épithéliales du poumon chez le cobaye à la suite d'injection d'un corynebacille diphtéroïde, Bull. Assoc. franç. p. l'étude du cancer **15**:212-237, 1926.

5. Löhlein, M.: Cystisch-papillärer Lungentumor, Verhandl. d. deutsch. path. Gesellsch. **12**:111-115, 1908.

The right hemithorax was smaller than the left, with bilaterally limited expansion and inspiratory retraction of the interspaces. The respirations were 20 to 40 per minute, shallow and labored. Impaired resonance and increased tactile fremitus were noted over the entire right side of the chest, especially posteriorly, and at the left base, with tubular breathing on the right over the posterior surface and a small area of the midlung field anteriorly. Numerous moist rales were audible over the entire chest. The spleen was not palpable, and there was no significant lymphadenopathy. The remainder of the physical findings seemed within the limits of normal.

The hemoglobin content was 15.4 Gm., and the white cell count 16,500, with 93 per cent neutrophils, 4 per cent lymphocytes and 3 per cent monocytes. The neutrophils all showed toxic changes, and there were many stab forms. The values for blood sugar and nonprotein nitrogen were normal, the results of routine urinalysis were not remarkable, and the Wassermann test of the blood was negative. Two sputum specimens examined did not show acid-fast bacilli.

A stereoscopic roentgenogram of the chest obtained April 20 was reported on as follows by Dr. L. W. Paul: "The heart is about in midposition. The right border is not well seen, but I doubt that it is enlarged. There is some soft patchy mottling throughout the left

Fig. 1.—Cut surface of the right lung. The absence of color contrast makes reproduction of detail unsatisfactory, but the extensive nodular involvement replacing almost the entire parenchyma except for the two dark areas in the upper lobe is visible. The pleura where seen is smooth and not involved by the adenomatous process.

middle and lower lung fields, although no large areas of consolidation are present here. The left dome of the diaphragm is smooth, and the sulcus is clear. On the right there is a great deal of soft opacity, almost completely obscuring the aerated lung except for some air in the apex and peripherally at the base. The peripheral part of the dome of the diaphragm is visible, with a clear sulcus. Medially the dome is obscured by pulmonary changes."

The course of illness in the hospital was that of an acute fulminating pneumonic process, with progressive dyspnea and cyanosis and increasingly numerous coarse moist rales obscuring other pulmonary auscultatory findings. There was a spiking temperature with a daily variation of 3 to 4 degrees and with peaks of 105 to 106 F., and the respiratory rate rose to about 50 per minute. The white blood cell count fell to a total of 3,700, with 88 per cent neutrophils, 10 per cent lymphocytes and 2 per cent monocytes. The patient became increasingly lethargic and confused, and died April 24, 1941.

Autopsy was performed four hours after death. Clubbing of fingers and toes, cyanosis and emaciation were again noted. The abdominal panniculus measured only 1 to 2 mm. in its thickest portion. There were early generalized arteriosclerosis and arteriolar nephro-

sclerosis and some slight residual myocardial changes from an earlier rheumatic fever. The only other significant changes were in the lungs and their associated lymph nodes.

Each pleural cavity contained about 100 cc. of serosanguineous fluid, and on the surface of the lower lobe of the right lung there were a few small granular fibrin deposits of recent origin. About the upper lobe of this lung and in the interlobar fissures of both lungs were a few fine fibrous adhesions. The lungs themselves seemed rather voluminous and did not collapse when removed.

The surface of the right lung was smooth, except as already noted, and pinkish gray, with anthracotic mottling. The lung was quite heavy and felt firm; it was subcrepitant and full of irregular nodules beneath the pleura. Its cut surface was in most areas pinkish yellow, smooth and meaty in appearance, with fine strands of gray-white tissue separating great numbers of closely packed round or polygonal nodules a few millimeters to several

Fig. 2.—Section from a subpleural nodule. The pleura is thickened but not invaded by the epithelial change. The normal alveolar framework is preserved and covered by a single layer of tall columnar cells, sometimes thrown up into papillary folds. The alveolar exudate is evident. Hematoxylin and eosin stain; × 10 objective and ocular.

centimeters in diameter. Here and there were small patches of what appeared to be congested and edematous but still crepitant and somewhat emphysematous lung tissue.

The left lung showed similar but much less extensive nodularity beneath a perfectly smooth pleura and was generally subcrepitant to crepitant except for purplish meaty consolidated areas posteriorly. The cut surface was moist, exuding quantities of pinkish frothy fluid, and showed numerous patchy areas resembling the bulk of the right lung. The intervening areas showed purplish meaty consolidation posteriorly and edema with alternating patchy atelectasis and emphysema anteriorly.

The trachea and the bronchi were filled with a frothy brownish fluid, and their mucosae were somewhat injected, but nowhere, as far as they could be followed, could any tumor growth be detected in them. The major vessels seemed normal except for slight atheromatous changes. The hilar and tracheobronchial nodes were slightly enlarged, moderately

firm, on section moist, and pale gray mottled with black; they showed no apparent neoplastic change.

On microscopic study the nodules seen grossly seemed to be formed by portions of lung tissue which retained their normal alveolar skeleton. The normal alveolar epithelium had been replaced by high cuboidal and columnar cells. Generally the alveoli were lined by only a single layer of cells; in one or two isolated spots there seemed to be a slight anaplastic tendency with the formation of tiny nests of polyhedral cells within an alveolar lumen. The cells were often so closely crowded together as to give a pseudostratified appearance, and in some areas they were pushed up into papillary folds supported on fine strands of stroma. An occasional mitotic figure was found in widely scattered areas. The epithelial cells themselves possessed granular cytoplasm, staining moderately heavily with eosin, and a large vesicular nucleus, usually located just below the middle of the cell but occasionally at either end. The

Fig. 3.—High power view (× 45 objective) of the nodule seen in figure 2. Hematoxylin and eosin strain.

nuclear membranes were quite heavy, and each nucleus contained one or two large nucleoli plus a few scattered chromatin threads and granules.

The stroma in general had the structure of the normal alveolar wall with slight fibrous thickening. In a few small areas interalveolar fibrosis was quite prominent, with bands of connective tissue as wide as the alveoli themselves. The vascular bed showed about the same degree of development as in normal pulmonary tissue, with no undue congestion. A few neutrophils and lymphocytes infiltrated the stroma, but this change was slight and no abnormal lymphoid accumulations were seen. A few laminated hyaline bodies, which were believed to be corpora amylacea, were noted. The involved alveoli contained small amounts of precipitated albuminoid material, with some mononuclear phagocytes, desquamated epithelial cells and an occasional neutrophil. There was little production of mucus in the adenomatous alveoli.

The areas of lung not involved by this process were mostly subject to an intense acute inflammatory edema and necrotizing bronchopneumonia of quite recent origin. The few small unaffected areas showed alternating patchy atelectasis and emphysema.

In no area could any involvement of the pleura, the bronchi, the blood vessels or the lymphoid structures be detected, in spite of careful and extensive study. The tracheobronchial tree showed only catarrhal inflammation, with an occasional respiratory bronchiole showing epithelial changes adjacent to an alveolar opening, and no larger divisions being affected anywhere. The pleura showed a slight general fibrous thickening but was nowhere invaded by epithelial growth. The hilar and bronchial lymph nodes showed small lymphoid follicles spread apart by sinuses distended with fluid containing strands of fibrin and large numbers of neutrophils and mononuclear phagocytes, but not the slightest evidence of neoplastic involvement.

Cultures of blood from the heart gave no bacterial growth, and only staphylococci were recovered from the pulmonary tissues. Careful microscopic study revealed no fungi, protozoa or wormlike parasites, and stains for acid-fast bacilli and Gram stains of lung tissue showed

Fig. 4.—Section stained by Mallory's technic for connective tissue. Note that the basic structure of the alveolar wall is not greatly altered from normal except for the epithelial change and slight fibrosis (× 45 objective).

only numerous cocci, primarily in the pneumonic areas. No inclusion bodies could be found in either nuclei or cytoplasm.

Because of the bizarre and unfamiliar gross appearances, advantage was taken of frozen sections at the necropsy table. The tumor-like appearance of the tissue led to careful search for evidence of primary or metastatic neoplastic involvement elsewhere in the body, but none could be detected. The picture strongly suggested that described by Ewing[6] under the heading "Infectious Adenomatosis of Lungs in Sheep," in which he noted its supposed virus etiology. Consequently, portions of lung tissue were given to Dr. A. F. Rasmussen Jr., of the department of bacteriology of the University of Wisconsin, who attempted to transmit any causative virus by inoculating animals with a 10 per cent suspension of the tissue mass

6. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 874.

which had been preserved in glycerin. One monkey received 6 cc. intranasally under deep anesthesia induced with ether. Two rabbits received 3 cc. each by intrapulmonic injection. Three guinea pigs were subjected to an atomized spray of 25 cc. of the tumor suspension in a small closed chamber for a period of six hours. Intrapulmonic inoculations were made into other guinea pigs. Two of the guinea pigs died after about two months but showed no evidence of adenomatous pulmonary change. The other animals all remained well, and when they were put to death after some months' observation, no pulmonary adenomas or other apparently related lesions could be found. Facilities for the use of sheep were not available.

Dr. E. V. Cowdry, who has made extensive studies of jagziekte and Montana progressive pneumonia of sheep, supplied us with several preparations from sheep lungs involved by jagziekte.

A comparison of those specimens with the involved tissues in our case emphasized their striking similarity in many respects. The pathologic changes in jagziekte have been repeatedly described in detail [7] and need not be reviewed here. The gross appearance, the basic histologic structure of the lesion, with retention of the normal pulmonary framework and total absence of destructive tendencies, the changes in the interstitial tissues, the absence of metastases and of invasion of the pleura or bronchi, the alveolar exudate and the epithelial hyperplasia described in the foregoing paragraphs are quite like those in the jagziekte sections available to us and those described in the literature. The individual epithelial cells in our case are not typical, however, those usually seen in jagziekte being less tall and having a somewhat clearer cytoplasm with a more darkly staining nucleus.

From the evidence available the lesions in the patient can be called only multiple pulmonary adenomatosis, and any suggestion as to their cause or their analogy to the changes of jagziekte in sheep must be purely speculative and without adequate support. The many parallel morphologic features and the absence of clearcut differentiating characteristics other than the dissimilarities in epithelial structure render such speculation tempting, however.

A few other isolated cases have been described in which the involvement corresponds more or less to the picture both in this patient and in sheep, while differing considerably from any other well known pulmonary lesion. Dungal [7c] reviewed the literature in search of such instances and cited reports by Löhlein,[5] Oberndorfer [8] and Helly.[9] The case of Helly seems almost identical with the present one except for a somewhat greater production of mucus in the affected alveoli. Oberndorfer's patient had very similar changes in the lungs, but metastases to bones and the regional nodes were present. (In this respect it may be noted that Aynaud,[10] whose sections were also studied by Dungal,[7c] found metastases in a single case of what was apparently true jagziekte in a sheep.) Löhlein's case histologically resembled Helly's but was limited to a single apple-sized tumor in the lower lobe of the right lung. In discussing Löhlein's report, Sternberg and Saltykow stated, without details, that they had each seen a somewhat similar tumor, while Oberndorfer also noted several reports by other workers of lesions possibly belonging to this group. Since Dungal's study, Bonne [11] has reported another case

7. (*a*) Cowdry, E. V.: Comparative Pathology of South African Jaagsiekte and Montana Progressive Pneumonia of Sheep, J. Exper. Med. **45**:571-585 (April) 1927; (*b*) Studies on the Etiology of Jaagsiekte, ibid. **42**:335-345 (Sept.) 1925. (*c*) Dungal, N.: Epizootic Adenomatosis of the Lungs of Sheep: Its Relation to Verminous Pneumonia and Jaagsiekte, Proc. Roy. Soc. Med. **31**:497-505 (March) 1938. Pallaske.[2]

8. Oberndorfer, S.: Zellmutationen und multiple Geschwulstenstehungen in den Lungen, Virchows Arch. f. path. Anat. **275**:728-737, 1930.

9. Helly, K.: Ein seltener primärer Lungentumor, Ztschr. f. Heilk. **28**:105-110, 1907.

10. Aynaud, M.: Origine vermineuse du cancer pulmonaire de la brebis, Compt. rend. Soc. de biol. **95**:1540-1542, 1926.

11. Bonne, C.: Morphological Resemblance of Pulmonary Adenomatosis (Jaagsiekte) in Sheep and Certain Cases of Cancer of the Lung in Man, Am. J. Cancer **35**:491-501 (April) 1939.

which seems identical with the present one and has discussed its possible relation to jagziekte. Still more recently Richardson [12] has briefly described an additional case which he feels is of this type. Bonne cited yet another report by Briese [13] of a seemingly related lesion, which, however, had metastasized to regional lymph nodes.

There seems to be a considerable gap between the lesions in such cases as these and the simple localized epithelial hyperplasia and metaplasia often seen as the result of the action on human lungs of infectious or irritant agents. It is possible that this gap is more apparent than real, and until considerably more is known about the genesis of the type of process in question it would be rash to venture an opinion on the point. One cannot, moreover, dismiss Grumbach's suggestion [4] that this type of change represents a nonspecific response to certain pulmonary irritants, in support of which he cited not only his own experiments but various pathologic descriptions of metaplasia of pulmonary epithelium. The close resemblance to jagziekte is suggestive, however, and Dungal, in a series of carefully conducted experiments, has shown clearly that that disease may be transmitted from sheep to sheep in the course of direct contact or by confinement of a healthy animal in a pen previously occupied by a diseased one. Attempts at artificial transmission of jagziekte by inoculation of affected tissue have been, with one possible exception, uniformly unsuccessful, as have efforts to find a causative bacterial agent (e. g., Dungal and Taylor [14]). Students of the disease seem increasingly to favor the hypothesis that a virus is the causative factor. If this belief is correct and if future observations confirm the parallelism of jagziekte in sheep with the lesions described as pulmonary adenomatosis in man, another hitherto unrecognized virus may be added to the list of infectious agents which can affect the human lung. Even more stimulating to speculation, if considered in connection with Dungal's demonstration of the transmissibility of the disease, is De Kock's [15] suggestion that jagziekte may represent a true neoplasm. His hypothesis would find some support in the metastases noted by Oberndorfer and Aynaud, as well as in the morphologic appearance of the tissues, but would require considerable additional evidence to be really tenable.

SUMMARY

A case of pulmonary adenomatosis in man resembling somewhat the disease jagziekte as found in sheep has been described. Current opinion suggests that jagziekte is an infectious disease, possibly of virus origin. A few similar human cases have been previously reported, so that it would seem that multiple bilateral pulmonary adenomas may occasionally develop in man, resembling morphologically those found in the ovine disease mentioned. While the evidence to support it is slight, there must be considered the possibility that this lesion as seen in sheep possesses neoplastic characteristics as well as transmissibility. The identity of the condition found in man with that found in sheep is not established by available evidence but further investigation seems indicated when opportunity presents.

12. Richardson, G. O.: Adenomatosis of the Human Lung, J. Path. & Bact. **51**:297-298 (Sept.) 1940.

13. Briese: Zur Kenntnis des primären Lungenkarzinoms, mit statistischen Angaben, Frankfurt. Ztschr. f. Path. **23**:48-55, 1920.

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UNUSUAL SOUNDS EMANATING FROM THE CHEST

CAUSE AND DIAGNOSTIC SIGNIFICANCE OF BUBBLING, CLICKING, CRUNCHING, KNOCKING AND TAPPING SOUNDS; WITH A REPORT OF TWO CASES OF INTERSTITIAL EMPHYSEMA OF LUNG AND MEDIASTINUM

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Bubbling, clicking, crunching, knocking and tapping sounds emanating from the chest are rarely encountered in civilian practice and their significance is not generally appreciated. With the current great military mobilization physicians will undoubtedly encounter these sounds in many instances of thoracic wounds in military personnel and in civilians. It appears pertinent, therefore, to emphasize their mechanism of production and their diagnostic significance.

Tapping, clicking and snapping metallic sounds were encountered by Rees and Hughes [1] and Smith [2] in soldiers with wounds of the left side of the chest during the last war. These sounds varied in intensity from ones audible only with the stethoscope applied over the precordium to those which could be heard 6 to 8 feet (183 to 244 cm.) from the patient. They were synchronous with the heart beat but varied in relation to the cardiac cycle. Some were audible only during systole, others only during diastole and others during both phases. They were related to respiration but varied also in their relation to the respiratory cycle. Some were heard or became louder during inspiration, others during expiration and others at midinspiration and midexpiration. It was thought by the original authors that a lesion of the left side of the chest was necessary. Munden [3] showed that these sounds were not peculiar to military personnel when he observed them in a civilian, and Lister [4] called attention to the importance of pneumothorax on the left side.

The diagnostic significance of these sounds is intimately associated with the mechanism of their production. The latter has been the subject of a good deal of debate. Smith [2] and Lister [4] attributed the sounds to the heart striking emphysematous blebs in the mediastinum, and in 1937 Hamman [5] reported 6 cases of spontaneous interstitial emphysema of the lung and mediastinum in which crunching and bubbling sounds were audible to both the patient and the physician. McGuire and Bean [6] later reported 2 more cases and gave an excellent review of the literature. Pneumothorax on the left side was present in some cases, but its presence was not necessary for the production of the sounds. An excellent

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study by Macklin [7] showed the mechanism of transportation of air along sheaths of pulmonary blood vessels from alveoli to the mediastinum. Gumbiner and Cutter [8] have recently emphasized the making of lateral roentgenograms of the chest as a diagnostic procedure in cases of pneumomediastinum in newborn infants. Scadding and Wood [9] noted clicking and cracking sounds in 4 cases of spontaneous pneumothorax and clicking sounds in 2 cases of induced pneumothorax. These authors discounted mediastinal emphysema as a cause in their cases and attributed the sounds to forceful separation of pleural surfaces by cardiac systole.

In 1929 Dr. John Barnwell and I became interested in the mechanism of production of these sounds when we noted them in patients with induced pneumo-

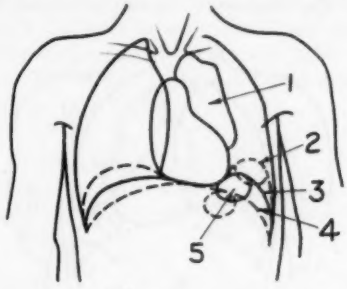

Fig. 1.—The diaphragm is in proper position during midinspiration and midexpiration for the heart to strike the gas bubble in the colon. *1*, collapsed lung; *2*, diaphragm during expiration; *3*, diaphragm during midinspiration and midexpiration; *4*, diaphragm during expiration, and *5*, gas bubble in colon.

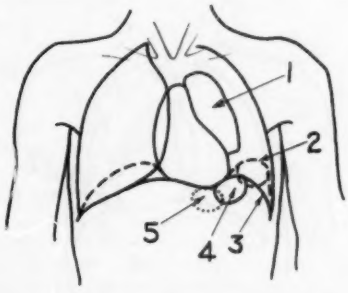

Fig. 2.—The diaphragm is in proper position during inspiration for the heart to strike the gas bubble in the colon. *1*, collapsed lung; *2*, diaphragm during expiration; *3*, diaphragm during inspiration; *4*, gas bubble in colon, and *5*, gas bubble in stomach.

thorax on the left side. Several of our patients were disturbed by these sounds when they lay in various positions at different periods after the injection of air into the pleural cavity. One day during preparations to reintroduce air into one of these patients a loud knocking metallic sound began to emanate from the patient's

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chest. The sound was audible at a distance of 3 feet (91 cm.), and several minutes later while I was listening with a stethoscope, borborygmus was heard and the sound disappeared. This occurred without introduction of more air into the pleural cavity or changing the position of the patient. It appeared likely, therefore, that the sound was related to the presence of gas in the bowel. Such sounds were made to reappear in this patient and in another by the injection of air into the colon in amounts sufficient to distend the splenic flexure. In another patient observed fluoroscopically during the presence of such sounds it was noted that they occurred simultaneously with the heart striking the diaphragm immediately above a large bubble of gas in the splenic flexure of the colon. These sounds were of a knocking metallic character, similar to those heard coming from the

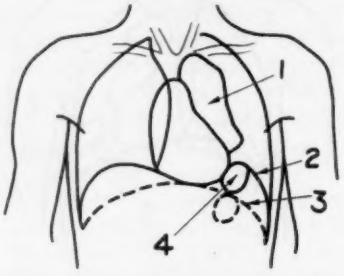

Fig. 3.—The diaphragm is in proper position during expiration for the heart to strike the gas bubble in the colon. *1*, collapsed lung; *2*, diaphragm during expiration; *3*, diaphragm during inspiration, and *4*, gas bubble in colon.

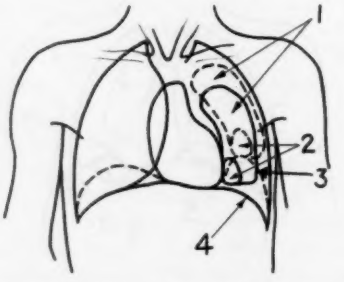

Fig. 4.—A large emphysematous bleb on the median aspect of the lung is in proper position to be struck by the uncushioned heart. *1*, collapsed lung; *2*, emphysematous bleb; *3*, diaphragm during expiration, and *4*, diaphragm during inspiration.

engine of a motor car during a hard pull. They were noted during systole in some instances and during diastole in others. They also occurred during different phases of respiration. If they were noted during inspiration, they persisted as long as inspiration was maintained. From our observation of several cases in which these sounds were noted at different times it appeared that those occurring during systole were due to rotation of the heart striking the diaphragm immediately above a bubble of gas in the colon. Those occurring during diastole were due to the free fling of the uncushioned heart in diastole striking the diaphragm as just described. The relation to the respiratory phase depended on the height of the diaphragm and its relation to the heart. The accompanying diagrams illustrate the relations of the heart, the diaphragm and a gas bubble in the colon to the production of the

sounds. It is to be noted that with the diaphragm at the normal level the sounds can be produced at midinspiration and midexpiration or at inspiration or at expiration. These sounds have been noted in association with varying degrees of collapse of the lung, from 25 to almost 100 per cent. The heart could strike an emphysematous bleb on the median aspect of a partially collapsed left lung and probably would produce a similar sound. It was thought that the mechanism of production of these sounds was due entirely to the process described here until similar sounds were heard in a case in which collapse of the lung was insufficient for the heart to strike the diaphragm and later in a case of pneumothorax on the right side. The sounds in these 2 cases, however, were different from the sounds previously observed. They were more clicking and tapping in character and were audible only with the stethoscope applied over the heart. It was thought, therefore, that there were different causes for the different types of sounds. It was not until I observed the patient in case 1 that the mechanism of the second type of sounds which we had heard became clear.

REPORT OF CASES

CASE 1.—A Negro physician aged 41 entered the University Hospitals on May 15, 1941, complaining of substernal pain and peculiar noises in his chest. He had enjoyed good health

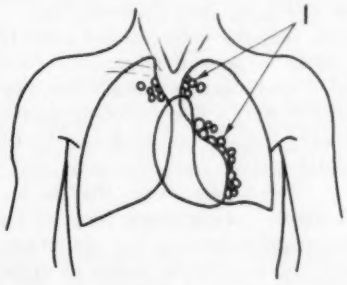

Fig. 5.—Interstitial emphysematous blebs (*1*) around the heart which cause bubbling, crunching and clicking sounds when they are struck by the heart.

until about 9 p. m. May 9 when while sitting at his desk he was seized suddenly with substernal pain which was severe and radiated to the left shoulder. There was no accompanying shortness of breath, palpitation of the heart, pallor or perspiration. He went to bed immediately and noted that lying on the left side produced more pain and caused tapping, crunching and bubbling sounds to come from the chest. These sounds were audible to his wife at the bedside and were synchronous with the heart beat. He soon found that lying on the right side with a pillow beneath the thorax caused the pain and sounds to disappear promptly. A roentgenogram of the chest was obtained the next morning and revealed nothing abnormal. He remained in bed until six days later, when he was admitted to the hospital. During this time he was comfortable when lying on his right side, but the pain and sounds promptly returned when he turned on his back or his left side. Physical examination revealed no evidence of pneumothorax. The heart was normal, but tapping and clicking sounds were audible with the stethoscope placed anywhere over the precordium. They were systolic in time and were loudest during midinspiration and midexpiration. The foregoing data were obtained with the patient in the sitting and in the supine position. When he lay on the left side, they were crunching and bubbling in character and were continuous throughout respiration but continued to be systolic in time. An anteroposterior roentgenogram of the chest failed to reveal any abnormality, but an oblique roentgenogram revealed evidence of air in the mediastinum. The pain and the sounds gradually subsided until they disappeared ten days after onset. The temperature, pulse rate and leukocyte count were normal.

CASE 2.—A white woman aged 21 entered the obstetric service of the University Hospitals on Jan. 4, 1942, for delivery of her second child after a full term pregnancy. During labor

on January 16 she strained forcefully with each uterine contraction, and during the latter part of labor she experienced a sharp pain over the precordium. The pain was not severe but prevented her from straining as hard as previously. The labor was normal, and she delivered a 7 pound (3,175 Gm.) normal baby. Immediately after labor a slight swelling and crepitation were noted in the neck by the attending physician. The heart sounds were distant, and synchronously with systole and diastole crackling sounds were heard which persisted when respiration was stopped. Approximately two hours later these sounds were crunching and bubbling in character, continued throughout the respiratory phase and were both systolic and diastolic in time. They became louder when the patient was turned on the left side, but at no time were they audible without application of the stethoscope to the precordium. The crepitation in the neck and the sounds gradually decreased, with the latter changing to tapping and clicking sounds before they disappeared five days after onset. There were no systemic reactions, and the patient was discharged on the tenth day post partum.

COMMENT

The clicking and tapping sounds in the 2 cases reported here were identical with those heard in the last 2 cases of pericardial knock associated with pneumothorax observed by Barnwell and myself. The crunching and bubbling sounds were not observed in the previous cases. In the 2 cases reported here pneumothorax was not present, and the sounds were typical of those occurring in interstitial emphysema of the lung and mediastinum. The bubbling, crunching, clicking and tapping sounds in these 2 cases were due undoubtedly to the heart striking emphysematous blebs in the lung and mediastinum. It appears logical from the data at hand to assume that the bubbling and crunching sounds are produced by fairly numerous or fairly large emphysematous blebs in close proximity to the heart, whereas clicking and tapping sounds are due to smaller and to less numerous blebs in the same vicinity. The knocking sounds, on the other hand, and probably some of the tapping sounds are produced by the heart striking a larger bubble of air located a little farther from the heart and separated from it by air free in the pleural cavity. The bubble of air may be an emphysematous bleb on the median aspect of a partially collapsed left lung or a gas bubble in the splenic flexure of the colon immediately beneath the diaphragm. The bubble must be at the proper distance from the heart to be struck an optimum blow by the rotation of the heart during systole or by the free diastolic fling of the uncushioned heart.

The clinical significance of these sounds has been discussed in part with the mechanism of production. Their occurrence indicates that interstitial emphysema of the lung or mediastinum or pneumothorax of the left side is present. The available data indicate that knocking or tapping metallic sounds occur in cases of pneumothorax of the left side, whereas bubbling, crunching and clicking sounds occur in cases of interstitial emphysema of the lung and mediastinum. These conditions may occur spontaneously, but they are usually due to trauma and they frequently coexist.

SUMMARY

Two cases of interstitial emphysema of the lung and mediastinum, spontaneous in 1 case and following straining in normal labor in the other, are reported. It is concluded that the bubbling, crunching, clicking and some of the tapping sounds are due to the heart rubbing against emphysematous blebs in interstitial emphysema of the lung and mediastinum. The knocking and tapping metallic sounds, on the other hand, are due to the heart striking an emphysematous bleb on the median aspect of a partially collapsed left lung or the diaphragm immediately over a gas bubble in the splenic flexure of the colon in the presence of pneumothorax of the left side. These conditions may occur spontaneously, or they may be due to trauma.

University Hospitals.

VALUE OF SODIUM CHLORIDE IN PREVENTION OF ALKALOSIS DURING "SIPPY" TREATMENT WITH CALCIUM CARBONATE

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Alkalosis can result from administration of soluble alkali [1] or from deprivation of chloride [2] or from both. It has been shown [3] also that the alkalosis observed during "Sippy" treatment with the administration of calcium carbonate is almost invariably associated with loss of gastric chloride and that in all probability the disturbance in the acid-base balance observed under these conditions is to be attributed to the loss of chloride rather than to calcium carbonate. If this thesis is correct, it should be possible to prevent the development of alkalosis by the administration of sodium chloride coincident with the administration of alkali. A study, therefore, was undertaken to determine the effect of the simultaneous administration of sodium chloride and calcium carbonate on the acid-base balance of a series of patients with peptic ulcer.

METHOD

Sodium chloride and calcium carbonate were given concurrently to 150 patients with peptic ulcer. Eight patients were given minimal amounts of magnesium carbonate as a laxative. The series comprised 116 men and 34 women of ages ranging from 24 to 76. The serum carbon dioxide, p_H and chloride and the blood urea nitrogen were measured at various intervals during therapy.[4] Renal function was estimated by the urea clearance test.[5]

RESULTS

Acid-Base Balance.—The acid-base balance remained normal except for temporarily increased p_H values for 135 of the 150 patients (table 1). Alkalosis occurred in 15 patients (10 per cent). The serum carbon dioxide ranged from 32.9 to 41.0 millimols per liter, exceeding 40 millimols per liter in 2 instances. The p_H varied from 7.47 to 7.63. The lowest values for serum chloride ranged from 81.3 to 99.7 millimols per liter; the values of 6 patients were between 81.3 and 90 millimols per liter, and those of 9 patients exceeded 90 millimols per liter. The acid-base disturbance was arbitrarily classified as mild in 9 patients, moderate in 4 and severe in 2.

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

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Clinical Aspects.—No direct relation existed between the amount of calcium carbonate ingested and the development of alkalosis. The total alkali intake of the 135 patients with normal serum electrolytes ranged from 200 to 500 Gm. for 104 patients and from 500 to 1,000 Gm. for 27 patients. The remaining 4 patients of this group received 1,148, 1,154, 1,850 and 2,355 Gm. of calcium carbonate, respectively. The total alkali intake of the patients in whom alkalosis developed varied from 200 to 500 Gm. for 9 patients and from 500 to 1,000 Gm. for 2 patients; 4 patients received 1,080, 1,144, 1,305 and 2,897 Gm., respectively. There was likewise no correlation between the amount of alkali given and the severity of the acid-base disturbance, for the alkalosis was mild in 3 of the 4 patients receiving the largest amounts of calcium carbonate.

Nine of the 15 patients with alkalosis did not have any complaints referable to the acid-base disturbance. The symptoms of the other 6 patients consisted of weakness, nausea, headache, dizziness and mental confusion.

In the group with normal serum electrolytes 9 patients had had massive hemorrhage, 9 had hypertension and 1 had polycythaemia rubra vera. Other complications in the group with alkalosis consisted of massive hemorrhage (3), hypertension (6), persistent secondary anemia (1) and perforated ulcer with diabetes (1).

TABLE 1.—*Acid-Base Balance During Simultaneous Administration of Sodium Chloride and Calcium Carbonate (One Hundred and Fifty Patients)*

	Serum CO_2 (mM/L)	Serum p_H	Serum Cl (mM/L)
No alkalosis (135 patients)	22-30	7.35-7.50	95-105
Alkalosis (15 patients)	32.9-41.0	7.47-7.63	81.3-99.7

TABLE 2.—*Urea Clearance at Beginning of Therapy with Sodium Chloride and Calcium Carbonate*

Urea Clearance	No Alkalosis	Alkalosis
Normal	94	4
Below normal	21	5
Undetermined	20	6
Totals	135	15

Renal Function.—Of the patients in whom alkalosis did not develop, the urea clearance of 94 at the beginning of treatment was normal, that of 21 was below normal and that of 20 was undetermined. Renal function of 8 patients in this group decreased temporarily during combined therapy with sodium chloride and calcium carbonate; originally, the urea clearance of 6 patients had been normal and that of 2 had been below normal.

In the group of patients in whom alkalosis developed the urea clearance at the onset of treatment was normal for 4, impaired for 5 and undetermined for 6 (table 2). Renal function during alkalosis was not altered significantly in 2 patients whose urea clearance had been normal originally. Renal function diminished during alkalosis in 8 patients; the clearance of 4 of them was below normal at the beginning of therapy. The values in 5 instances dropped to levels as low as 7, 11, 15, 19, and 20 per cent of average normal. The urea clearance subsequently returned to its original level in 7 of the 8 patients (undetermined for 1) in whom it had decreased. Renal function of 5 patients was not measured during alkalosis (table 3).

Blood Urea Nitrogen.—The blood urea nitrogen increased during alkalosis in 10 patients. The maximum values for 6 ranged from 16.2 to 30 mg. per hundred cubic centimeters and for 4 from 35.8 to 97 mg. per hundred cubic centimeters. The highest value for blood urea nitrogen (97 mg. per hundred cubic centimeters) was that of a 66 year old man with hypertension and urinary retention secondary to prostatic obstruction. Hypertension was present in the 4 patients with the highest values for blood urea nitrogen. The urine of 4 patients undergoing treatment contained slight to moderate amounts of albumin and hyaline and granular casts. Albumin and casts were present in the urine of 1 of these patients before treatment.

TABLE 3.—*Urea Clearance During Therapy with Sodium Chloride and Calcium Carbonate*

Urea Clearance	No Alkalosis	Alkalosis
Unchanged	92	2
Reduced	8	8
Undetermined	35	5
Totals	135	15

TABLE 4.—*Gastric Retention*

Volume (Cc.)	No Alkalosis	Alkalosis
0-100	81	0
100-200	30	3
200-300	12	3
300-400	9	2
400-500	1	5
500-	2	2
Totals	135	15

TABLE 5.—*p_H of Urine Before and After Administration of Sodium Chloride to Six Normal Infants* *

Before	After
5.80	7.35
6.75	6.40
6.75	7.10
6.35	6.75
5.90	6.00

* Data taken from Schoenthal.[7]

Gastric Retention.—A significant difference existed between the patients with normal serum electrolytes and those in whom alkalosis developed with respect to the volume of gastric contents aspirated daily (table 4). The amount aspirated averaged less than 200 cc. for 111 (81 per cent) of the patients without alkalosis but for only 3 (20 per cent) of those with alkalosis. Large quantities of acid gastric juice thus were removed daily from 12 (80 per cent) of the patients in whom alkalosis occurred. The loss of chloride via gastric aspiration appeared to be of considerable importance in the pathogenesis of hypochloremia and alkalosis, since in these persons presumably from 0.5 to 2.0 Gm. of chloride ion contained in the gastric contents, as well as a considerable portion of the sodium chloride given orally, was thereby removed each day. In view of the absence of changes in the serum electrolytes in some patients in whom marked gastric retention also was

present and whose intake of sodium chloride was no greater than that of patients with alkalosis, it would seem that the loss of chloride in the group with alkalosis had not been completely replaced by therapy with salt.

Sodium Chloride Therapy.—Of the patients in whom alkalosis did not develop, the daily intake of sodium chloride (in addition to the salt in the diet) averaged 4 to 5 Gm. for 61 patients and 5 to 10 Gm. for 74 patients. The daily intake of sodium chloride of the 15 patients in whom alkalosis developed averaged 3 to 5 Gm. for 7 patients and 5 to 10 Gm. for 8 patients.

SUMMARY OF FIFTEEN CASES OF ALKALOSIS OCCURRING DURING ANTACID THERAPY

CASE 1.—A. F., a 31 year old man with a stenosing duodenal ulcer, was found on admission to have a serum carbon dioxide of 33 millimols per liter. The blood urea nitrogen and the urea clearance were normal. There was moderately severe secondary anemia. Gastric contents obtained by aspiration averaged 457 cc. daily. Mild alkalosis was detected on the thirteenth day of treatment; the urea clearance decreased moderately during the acid-base disturbance. The serum electrolytes and the renal function returned to normal after the daily intake of sodium chloride (5 to 8 Gm.) had been increased to 10 Gm.

CASE 2.—A. J., a 43 year old man, received a total of 2,897 Gm. of calcium carbonate in forty-eight days. Gastric aspirations over a period of forty-one days averaged 400 cc. daily. Mild chemical alkalosis was noted on the twentieth day of therapy; the urea clearance was normal. The intake of sodium chloride (3 to 5 Gm.) was increased to 10 Gm. daily, and the acid-base balance returned to normal in seven days.

CASE 3.—G. K., a 39 year old man with diabetes and a large gastric ulcer, was first treated by continuous Wangensteen aspiration of the gastric contents for six days. The serum electrolytes were maintained by parenteral injections of physiologic solution of sodium chloride. A total of 1,305 Gm. of calcium carbonate was administered in the succeeding forty-four days; 10 Gm. of sodium chloride was given by mouth daily. The blood urea nitrogen and the urea clearance were normal prior to alkali therapy. Mild chemical alkalosis was noted on the thirteenth and the twenty-third day of hospitalization (the seventh and the seventeenth day of alkali therapy). The blood urea nitrogen and the urea clearance remained normal, however. Despite the continuation of alkali therapy the acid-base balance returned to normal.

CASE 4.—S. M., a 43 year old man, received a total of 588 Gm. of calcium carbonate in twenty days. Gastric contents obtained by aspiration over a period of eighteen days averaged 400 cc. daily. The original value for urea clearance was slightly reduced. Moderate alkalosis was noted on the sixth day of treatment; the patient had been vomiting for two days previously. The acid-base disturbance became severe on the twelfth day; the blood urea nitrogen increased to 17.4 mg. per hundred cubic centimeters, and the urea clearance fell to 43 per cent of average normal. The daily intake of sodium chloride (4 to 8 Gm.) was increased to 10 Gm., and on the fourteenth day 200 cc. of a 2 per cent solution of sodium chloride was given intravenously; calcium carbonate therapy was continued. The serum electrolytes and the blood urea nitrogen returned to normal in seven days; the urea clearance simultaneously returned to its original level.

CASE 5.—L. L., a 45 year old man with hypertension, was placed on antacid therapy ten days before entry into the hospital and on admission was found to be in a state of mild alkalosis. The blood urea nitrogen three weeks previously had measured 21.4 mg. per hundred cubic centimeters; the urea clearance was not determined. The alkalosis became moderately severe after six days, at which time the blood urea nitrogen had risen to 50 mg. per hundred cubic centimeters and the urea clearance had decreased to 20 per cent of average normal. Gastric contents obtained by aspiration over a period of fourteen days had averaged 328 cc. daily. The intake of sodium chloride (3 to 5 Gm.) was increased to 10 Gm. daily, and 5 per cent dextrose in physiologic solution of sodium chloride was given parenterally for two days; calcium carbonate therapy was continued. The acid-base balance was restored approximately to normal in five days. Three and one-half months later, despite continued alkali therapy, the serum electrolytes were normal; the blood urea nitrogen measured 10.8 mg. per hundred cubic centimeters, and the urea clearance was 65 per cent of average normal.

CASE 6.—D. H. S., a 53 year old man with hypertension, had experienced a massive hemorrhage from a duodenal ulcer shortly before admission to the hospital. He was markedly

anemic. Renal function was not measured prior to alkali therapy. A total of 390 Gm. of calcium carbonate was given in seventeen days. Gastric contents obtained by aspiration averaged 220 cc. daily. Mild chemical alkalosis was noted on the third day of therapy; the acid-base disturbance became severe on the fifteenth day, at which time the blood urea nitrogen rose to 27 mg. per hundred cubic centimeters and the urea clearance decreased to 20 per cent of average normal. In addition to the 10 Gm. of sodium chloride taken by mouth daily large amounts of physiologic solution of sodium chloride were given parenterally on the third, the seventh, the sixteenth, the seventeenth and the eighteenth day of therapy. The acid-base balance on the twenty-second day was normal despite continued ingestion of alkali. Three weeks later, the blood urea nitrogen measured 13.5 mg. per hundred cubic centimeters and the urea clearance was 70 per cent of average normal.

CASE 7.—P. L., a 40 year old man with a stenosing duodenal ulcer and hypertension, was found on admission to be in a state of mild alkalosis. The acid-base balance was restored to normal after three infusions of 1,500 cc. of physiologic solution of sodium chloride. A total of 414 Gm. of calcium carbonate was given subsequently. Gastric contents obtained by aspiration averaged 800 cc. daily. Eight grams of sodium chloride was given by mouth daily. Mild chemical alkalosis was noted on the seventh day of alkali therapy, but the serum electrolytes returned to normal without additional treatment.

CASE 8.—F. S., a 54 year old man with a stenosing duodenal ulcer, had moderately severe alkalosis on the fourth day of alkali treatment. Gastric contents obtained by aspiration had averaged 490 cc. daily. Renal function was not measured prior to therapy; during alkalosis, however, the urea clearance was only slightly below normal. The acid-base balance was partially restored after the intake of sodium chloride by mouth had been increased from 5 to 15 Gm. daily and physiologic solution of sodium chloride had been administered on the fourth and the fifth day of treatment. Tri-calsate[6] was substituted for calcium carbonate on the fourteenth day of therapy, and the serum electrolytes returned to normal. The blood urea nitrogen and the urea clearance were normal after subsidence of the alkalosis.

CASE 9.—F. O'T., a 53 year old man with syphilis and hypertension, had vomited frequently prior to admission to the hospital. A total of 328 Gm. of calcium carbonate was given in eleven days. Gastric contents obtained by aspiration averaged 195 cc. daily. Renal function was not measured prior to alkali therapy. Mild chemical alkalosis was noted on the ninth day of therapy; the blood urea nitrogen increased to 24.8 mg. per hundred cubic centimeters, and the urea clearance dropped to 10 per cent of average normal. Alkali therapy was discontinued for three days, and the daily intake of sodium chloride was increased from 5 to 10 Gm.; 3,000 and 1,300 cc. of physiologic solution of sodium chloride were administered parenterally on two occasions. The acid-base balance returned to normal and was not altered after the resumption of calcium carbonate therapy.

CASE 10.—J. McI., a 41 year old man with syphilis and hypertension, had taken large amounts of sodium bicarbonate for the relief of symptoms of ulcer. On entry, the blood urea nitrogen measured 23.3 mg. per hundred cubic centimeters and the urea clearance 60 per cent of average normal. A total of 212 Gm. of calcium carbonate was given during the first seventeen days; 3 Gm. of sodium chloride was taken by mouth daily. Gastric contents obtained by aspiration averaged 230 cc. daily. Moderately severe alkalosis was noted on the sixth day of treatment. The blood urea nitrogen measured 29.8 mg. per hundred cubic centimeters and the urea clearance 22 per cent. From 1,500 to 3,000 cc. of physiologic solution of sodium chloride was given daily from the sixth to the tenth day of therapy. Calcium carbonate therapy was discontinued, and aluminum hydroxide alone was administered during the next sixteen days. The acid-base balance returned to normal, although the blood urea nitrogen continued to range from 18.2 to 27.0 mg. per hundred cubic centimeters. Calcium carbonate therapy was resumed on the thirty-fourth day of hospitalization; 6 Gm. of sodium chloride was given by mouth daily. The serum electrolytes remained normal except for a slight elevation of the serum carbon dioxide (32.8 millimols per liter). One month later, the blood urea nitrogen measured 20.7 mg. per hundred cubic centimeters and the urea clearance 40 per cent of average normal.

CASE 11.—T. D., a 66 year old man, entered the hospital because of a massive hemorrhage from a duodenal ulcer. Seven blood transfusions and 1,144 Gm. of calcium carbonate were administered in twenty-nine days. Five grams of sodium chloride was given by mouth daily. The clinical course was complicated by the development of urinary retention. Mild

6. Tri-calsate is a proprietary antacid which when in aqueous solution consists essentially of tribasic calcium phosphate and sodium citrate.

alkalosis was noted on the second day. The alkalosis became severe on the twenty-sixth day. At this time, the blood urea nitrogen rose to 97 mg. per hundred cubic centimeters and the urea clearance diminished to 7 per cent of average normal (renal function had been impaired originally). Gastric contents obtained by aspiration between the twenty-first and the thirty-first day averaged 502 cc. daily. The serum electrolytes returned to normal after the daily administration of 3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride and of saline solution alone. Alkali therapy and gastric aspiration were discontinued on the thirty-first day of hospitalization. The blood urea nitrogen gradually decreased to 12.8 mg. per hundred cubic centimeters, and the urea clearance one month later rose to 60 per cent of average normal, its original level.

CASE 12.—F. C., a 48 year old man with hypertension, was admitted to the hospital with a massive hemorrhage from a duodenal ulcer. A total of 734 Gm. of calcium carbonate was given in twenty-nine days. Gastric contents obtained by aspiration averaged 168 cc. daily. Before treatment urea clearance was slightly below normal. Symptoms suggestive of alkalosis were noted on the twenty-fourth day of hospitalization, at which time the daily intake of sodium chloride (3 to 6 Gm.) was increased to 10 Gm. Mild chemical alkalosis was noted on the twenty-sixth day, and 1,500 cc. of physiologic solution of sodium chloride was given parenterally. Calcium carbonate therapy was discontinued on the thirtieth day, at which time the blood urea nitrogen measured 31.2 mg. per hundred cubic centimeters and the urea clearance 15 per cent of average normal. The blood urea nitrogen returned to normal and the urea clearance to its original level several weeks later.

CASE 13.—L. B., a 48 year old man, had been vomiting frequently for six to seven months. The urea clearance was not determined before alkali therapy was begun. Gastric contents obtained by aspiration over a period of twenty days averaged 300 cc. daily. Severe alkalosis was noted on the ninth day of therapy; the daily intake of sodium chloride was increased from 5 to 8 Gm., with prompt clinical relief.

CASE 14.—H. F., a 55 year old man, had vomited frequently before hospitalization. Large amounts of gastric contents were aspirated daily. The original value for urea clearance was low. Mild alkalosis was noted on the eleventh day. The intake of sodium chloride was maintained at a level of 10 Gm. daily. There were no clinical symptoms. The acid-base balance was not determined subsequently.

CASE 15.—J. G., a 44 year old man with normal renal function, was found to have mild chemical alkalosis on the eighth day of alkali therapy. The serum electrolytes were not measured subsequently. There were no clinical symptoms.

COMMENT

The results of this investigation indicate that alkalosis complicating "Sippy" treatment with calcium carbonate can be prevented in almost all patients by the concurrent administration of adequate amounts of sodium chloride. The therapeutic action of sodium chloride is probably attributable (*a*) to the replacement of chloride ion lost by the aspiration of gastric contents and (*b*) to the increased excretion of base bicarbonate in the urine at the expense of the blood bicarbonate after the administration of salt. The experimental observations of Schoenthal[7] are of particular importance in this connection. Hartmann and Smyth[8] had shown previously that in the presence of an increased level of plasma bicarbonate secondary to loss of chloride the administration of sodium chloride leads to the excretion of bicarbonate in the urine. Schoenthal gave 6 healthy infants 6 to 10 Gm. of sodium chloride daily, distributed equally in the feedings over a period of one to four days. An increase in the chloride concentration of the serum of 6 to 15 per cent was observed in all infants. The plasma bicarbonate decreased moderately in 4 infants, and the reaction of the plasma of 3 infants tended to shift toward the acid side. The excretion of base bicarbonate in the urine was usually increased and accompanied by a rise in p_H, as shown in table 5. There was naturally an increase in the urinary

7. Schoenthal, L.: Acid-Base Metabolism: Effects of Administration of Salt and of Restitution of Water, Am. J. Dis. Child. **37**:244 (Feb.) 1929.

8. Hartmann, A. F., and Smyth, F. S.: Chemical Changes in the Body Occurring as a Result of Vomiting, Am. J. Dis. Child. **32**:1 (July) 1926.

chloride, but this did not equal the intake. These data are in agreement with the observations of György [9] in his study of excretion of acid by infants after the administration of sodium chloride.

It should be noted that in several patients of the present series sodium chloride therapy was apparently not only inadequate to forestall the development of alkalosis but insufficient to correct the acid-base disturbance. It is possible that to these few patients insufficient amounts of salt were given and also that the excretion of bicarbonate in the urine was retarded by antecedent impairment of renal function.

CONCLUSIONS

Administration of sodium chloride during "Sippy" treatment with calcium carbonate decreased the incidence of alkalosis from 30 to 10 per cent.

This type of alkalosis is due to the loss of chloride (gastric aspiration) and can be prevented by the administration of sufficient amounts of sodium chloride.

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9. György, P.: Zur Frage der Säureausscheidung im Urin, Ztschr. f. d. ges. exper. Med. **43**:443, 1924.

Progress in Internal Medicine

DISEASES OF NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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Because of the pressure of work occasioned by the war this year's review on diseases of nutrition must be abbreviated. It represents, in fact, little more than a compilation of casual reading in the field. Important items undoubtedly have escaped attention.

We are happy to be able to inform our readers of the appearance in November 1942 of the first issue of a new journal called *Nutrition Reviews*. This publication has been undertaken by the recently created Nutrition Foundation, Inc., New York. The editorial staff of the new journal has been carefully selected and justifies the confidence of members of the medical profession and other persons engaged in application of nutritional knowledge. Issues will appear monthly. It is proposed to bridge the gap between substantial research findings and their acceptance on the part of those persons who have responsibility for application of the best of what is new. The reviews must be critical in their appraisals of material if this purpose is to be accomplished, and to judge from the contents of the first issue critical appraisal can be expected. The subscription price is nominal. Much of the literature on nutrition is not to be found in journals which customarily are available to physicians. The issues of *Nutrition Reviews* as they appear are intended to provide authoritative, unbiased, editorially interpreted reviews of the world's progress in the science of nutrition and since this science applies to almost every field of medicine, *Nutrition Reviews* should be a welcome addition to the libraries of physicians.

GENERAL PROBLEMS

With the coming of war the nutritional problems of the armed forces, the industrial workers and the general populace have assumed critical importance. The nutritional problems of the Army have received much attention.[1] In an excellent paper Keys and Henschel [2] reported a comprehensive study made on a group of soldiers from the United States Army to determine the effect of various vitamin supplements on muscular ability, endurance, resistance to fatigue and recovery from fatigue. It was found that thiamine, riboflavin, niacin (nicotinic acid),

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1. Tobey, J. A.: The Army's Nutritional Problems, War Med. **2**:437-444 (May) 1942. Howe, P. E.: Nutritional Problems of the Army, Mil. Surgeon **90**:253-266 (March) 1942. Epstein, M. H.: The Nutrition of the Soldier, ibid. **89**:872-877 (Dec.) 1941.

2. Keys, A., and Henschel, A. F.: Vitamin Supplementation of U. S. Army Rations in Relation to Fatigue and the Ability to Do Muscular Work, J. Nutrition **23**:259-269 (March) 1942.

pyridoxine, pantothenic acid and ascorbic acid, when administered for four to six weeks, did not have any effects, favorable or otherwise, on brief extreme exercise, on prolonged severe exercise and in semistarvation on the muscular ability of these previously well nourished persons. It was found that the young men expending an average of 4,200 calories per day were not benefited by a daily supply of more than 1.7 mg. of thiamine hydrochloride, 2.4 mg. of riboflavin and 70 mg. of ascorbic acid. The investigators concluded that no useful purpose would be served by enrichment of the present garrison rations of the United States Army with the vitamins studied.

In the industrial field Schnedorf and his associates [3] were unable to find much evidence for vitamin deficiency disease in a survey of 1,265 healthy men. On the other hand, preliminary surveys made by a committee of the National Research Council [4] revealed deplorable conditions among persons engaged in war work in many plants. The following recommendations were made:

1. Nutritious meals of natural foods at prices the workers are accustomed to and can afford to pay should be made available in all plants engaged in production for war or defense purposes, except in small plants where the worker may obtain such meals from private sources in the free time at his disposal. Any meal served in the plant should contribute at least one-third of the daily requirements of specific nutrients recommneded by the Food and Nutrition Board of the National Research Council.

2. The practice of serving food between meals to workers has given good results and is recommended. Milk, fruit and tomato juices are to be preferred as beverages, and other foods which are served should include the necessary nutrients. Thus, when bread is served it should be enriched white bread or a whole grain product.

3. Choice of foods served in the plant should be determined by a trained dietitian or nutritionist. Brief study of workers' diets will enable the dietitian to make up menus calculated to compensate for the ordinary inadequacies. The employment of a dietitian or nutritionist by the plant is recommended. In cases where this is not feasible, advice may be obtained from the state or local Committee on Nutrition.

4. Suitable educational material should be presented in connection with cafeteria service or supplementary lunches to stimulate acceptance of the meals planned or the selection of good meals when there is a choice of foods. Such material should be so planned as to lead to the development of good health habits and should avoid undue emphasis on any particular food.

5. Measures should be taken by the appropriate subdivision of government to condition nutritionally those classes of the population which are likely to become workers in war or defense industries. Such nutritional conditioning might well be carried out among organized groups such as are found in CCC camps, NYA, WPA and Defense Training Schools. The large percentage of young men found to be unfit for service in the armed forces emphasizes the need for such conditioning, for employment in war industries may be just as strenuous and in far less favorable environment than service in the armed forces. Such work, already under way in this country, should be greatly extended.

The observation was reported [5] that administration of the vitamin B complex improved the working capacity in occupations in which fatigue, attributable to fatigue of the central nervous system, occurred. However, the Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association pointed out [6] that satisfactory evidence is lacking of the wisdom of the general practice of industrial concerns of indiscriminately providing all of their

3. Schnedorf, J. G.; Weber, C. J., and Clendening, L.: A Vitamin Survey of Normal Industrial Workmen, Am. J. Digest. Dis. **9**:188-191 (June) 1942.

4. The Food and Nutrition of Industrial Workers in Wartime, Committee on Nutrition in Industry, National Research Council, Reprint and Circular Series, no. 110, April 1942.

5. Simonson, E.; Enzer, N.; Baer, A., and Braun, R.: The Influence of Vitamin B (Complex) Surplus on the Capacity for Muscular and Mental Work, J. Indust. Hyg. & Toxicol. **24**:83-90 (April) 1942.

6. Indiscriminate Administration of Vitamins to Workers in Industry, report of the Council on Foods and Nutrition and the Council on Industrial Health, J. A. M. A. **118**:618-621 (Feb. 21) 1942.

employees with vitamins. This report emphasized the need for avoidance of the indiscriminate mass use of vitamins, a practice which supports commercial exploitation rather than scientific rational use of these important dietary factors.

The civilian population is beset with nutritional problems. From a rather extensive survey Jolliffe, McLester and Sherman [7] concluded that dietary inadequacies and malnutrition of varying degrees are of frequent occurrence in the United States and that the nutritional status of an appreciable part of the population can be distinctly improved. They pointed out that if optimal nutrition, not merely adequate nutrition, is sought, then widespread improvement is possible.

As clearly pointed out by Ruffin,[8] both the public and the members of the medical profession have become overenthusiastic on the subject of vitamins, and there is a rapidly growing tendency today to attribute most of the ills of the human race to vitamin deficiency. This author emphasized that when specific deficiencies occur, response to specific therapy is rapid, and if the patient does not show any improvement after three or four weeks of treatment, there seems little justification in allowing him to buy preparations of vitamins, especially those containing the vitamin B complex. In his experience treatment of patients suspected of having a mild deficiency with single members of the vitamin B complex have been most disappointing. In a recent editorial [9] the use of many so-called "shotgun" vitamin preparations was condemned. On the other hand, the Council on Foods and Nutrition of the American Medical Association [10] has approved and will accept for listing in New and Nonofficial Remedies multivitamin preparations in which the proportions of the various vitamins included bear a direct relation either to the minimal requirements promulgated by the Food and Drug Administration or to the recommended daily allowances of the Food and Nutrition Board of the National Research Council. A multivitamin preparation used by the armed forces as a dietary supplement in emergencies, when rations may be inadequate, contains vitamin A 2,500 international units, vitamin D 200 U. S. P. units, vitamin B_1 1 mg., riboflavin 1.5 mg., niacin amide 10 mg. and ascorbic acid 37.5 mg. These values represent approximately half the daily recommended allowances of the Food and Nutrition Board for men consuming 3,000 calories of food.

During the past year several reviews on various phases of nutrition have appeared and bear reading.[11]

VITAMIN A

Chemistry and Physiology.—The excretion of vitamin A appears to be highly selective. Lawrie and his associates [12] reported that vitamin A is associated in urine with only minute amounts of lipoids. In human urine vitamin A is absent in health but present in association with some pathologic conditions, particulary pneumonia, chronic nephritis and nephrosis. In pneumonia the daily excretion of vitamin A sometimes exceeds 3,000 international units. When vitamin A was given orally

7. Jolliffe, N.; McLester, J. S., and Sherman, H. C.: The Prevalence of Malnutrition, J. A. M. A. **118**:944-950 (March 21) 1942.

8. Ruffin, J. M.: The Diagnosis and Treatment of Mild Vitamin Deficiencies: A Clinical Discussion, J. A. M. A. **117**:1493-1496 (Nov. 1) 1941.

9. Shotgun Vitamins Rampant, editorial, J. A. M. A. **117**:1447 (Oct. 25) 1941.

10. The Proper Use of Vitamins in Mixtures, report of the Council on Pharmacy and Chemistry and Council on Foods and Nutrition, J. A. M. A. **119**:948-949 (July 18) 1942.

11. Williams, R. J.: The Approximate Vitamin Requirements of Human Beings, J. A. M. A. **119**:1-3 (May 2) 1942. Starr, P.: The Value of Vitamins in Surgical Practice: Collective Reviews, Internat. Abstr. Surg. **74**:309-322 (April) 1942. Jeghers, H.: Nutrition, New England J. Med. **225**:687-697 (Oct. 30) 1941. György, P.: The Water-Soluble Vitamins, Ann. Rev. Biochem. **11**:309-364, 1942.

12. Lawrie, N. R.; Moore, T., and Rajagopal, K. R.: Excretion of Vitamin A in Urine, Biochem. J. **35**:825-836, 1941.

to human beings, 88 to 96 per cent of it failed to be accounted for in the blood and the feces. However, after ingestion of large doses of vitamin A a substance was found in the blood and the feces which seemed to be a closely related oxidation product.[13]

Feller and his associates,[14] in a critical study of the influence of vitamin A and vitamin C on immunologic reactions in human beings, found little to support the view that vitamin A or ascorbic acid affects so-called "resistance to infection."

Methods of Measuring Vitamin A Deficiency.—The controversy on the value of measuring deficiency of vitamin A by dark adaptation tests continues. However, the opinion that the test of adaptation to darkness does not sharply identify cases of mild vitamin A deficiency is gaining favor.[15] With refinements in methods of measuring vitamin A in the blood have come studies which indicate that this method is more sensitive as an indicator of vitamin A deficiency. It seems to be promising, although more data are needed to establish the range of normal and of abnormal values.[16] Yudkin[17] reported that both alcohol and amphetamine sulfate may produce transient improvement in adaptation to darkness without any corresponding increase in the concentration of vitamin A in the blood. Kruse[15c] refutes the charge that changes in adaptation to darkness preceded conjunctival changes noted by him in many cases of vitamin A deficiency. In more than 100 persons who did not have impaired adaptation to darkness he observed gross or microscopic changes in the conjunctivas. These changes slowly disappeared after administration of vitamin A. As was mentioned in last year's review, Kruse maintained that under ordinary conditions conjunctival changes probably precede dysadaptation in avitaminosis A.

Clinical Deficiencies.—A summary of the clinical conditions associated with vitamin A deficiency was published by Mandelbaum.[18] Administration of vitamin A in doses of 25,000 to 50,000 international units daily for three to eight weeks was reported to have enabled color-blind patients to pass a standard color vision test in which they previously had failed.[19] The permanence of this improvement remained to be determined. The levels of vitamin A in the plasma of patients with cancer of the gastrointestinal tract were found to be below the normal range in 86

13. LePage, G. A., and Pett, L. B.: Absorption Experiments with Vitamin A, J. Biol. Chem. **141**:747-761 (Dec.) 1941.

14. Feller, A. E.; Roberts, L. B.; Ralli, E. P., and Francis, T., Jr.: Studies on the Influence of Vitamin A and Vitamin C on Certain Immunological Reactions in Man, J. Clin. Investigation **21**:121-137 (March) 1942.

15. (*a*) Oldham, H.; Roberts, L. J.; MacLennan, K., and Schultz, F. W.: Dark Adaptation of Children in Relation to Dietary Levels of Vitamin A, J. Pediat. **20**:740-752 (June) 1942. (*b*) Hunt, E. P., and Hayden, K. M.: Medical Evaluation of Nutritional Status: IX. The Reliability of Visual Threshold During Dark Adaptation as a Measure of Vitamin A Deficiency in a Population Group of Low Income, Milbank Memorial Fund Quart. **20**:139-168 (April) 1942. (*c*) Kruse, H. D.: Methods of Detecting Mild Cases of Vitamin A Deficiency, Science **95**:623-624 (June 19) 1942.

16. Bodansky, O.; Lewis, J. M., and Haig, C.: The Comparative Value of the Blood Plasma Vitamin A Concentration and the Dark Adaptation as a Criterion of Vitamin A Deficiency, Science **94**:370-371 (Oct. 17) 1941. Lewis, J. M.; Bodansky, O., and Haig, C.: Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and in Children, Am. J. Dis. Child. **62**:1129-1148 (Dec.) 1941. Yarbrough, M. E., and Dann, W. J.: Dark Adaptometer and Blood Vitamin A Measurements in a North Carolina Nutrition Survey, J. Nutrition **22**:597-607 (Dec.) 1941.

17. Yudkin, S.: Vitamin A and Dark-Adaptation Effect of Alcohol, Benzedrine and Vitamin C, Lancet **2**:787-791 (Dec. 27) 1941.

18. Mandelbaum, J.: Vitamin A: Some Clinical Considerations, M. Clin. North America **26**:965-984 (May) 1942.

19. Dunlap, K., and Loken, R. D.: Vitamin A for Color-Blindness, Science **95**:554 (May 29) 1942.

per cent.[20] Although administration of yeast and of lipocaic, which are free of carotenoids, raised the levels of vitamin A in the plasma of these patients, hepatic dysfunction was not believed to be the cause of the low levels.[21] Absorption of vitamin A by patients who have pulmonary tuberculosis also is impaired,[22] but the derangements of function responsible are not known.

The intimate and important role of the liver in metabolism of vitamin A continues to be emphasized.[23] It has long been known that an injured hepatic parenchyma contains less vitamin A than normal hepatic parenchyma and is less able to handle carotenoid metabolism. It is reported that abnormal adaptation to darkness was exhibited in 90 per cent of a group of 20 cases of cirrhosis of the liver, although clinical night blindness was present in only 16 per cent.[24] The level of vitamin A in the blood of 90 per cent of patients with cirrhosis of the liver and of carotenoid in the blood of 50 per cent of them was below the lowest normal values.[25] A large dose of vitamin A (100,000 international units) administered to a patient with cirrhosis of the liver is said to be followed by a smaller rise in the plasma level of vitamin A than occurs in a normal subject.[26] A test of this type may serve as an index of vitamin A deficiency in a patient with disease of the liver.

THIAMINE

Chemical and Physiologic Properties.—The average level of thiamine in the normal leukocyte was reported to be ten times that in the normal erythrocyte,[27] a distribution similar to that of riboflavin and of ascorbic acid. The greater concentrations in leukocytes may be explained by the fact that these cells are more actively metabolizing tissue than the other components of blood. An increase in urinary excretion of pyrimidine follows the parenteral administration of thiamine, and it is believed that this substance is derived from thiamine. Evidence also was presented to show that thiamine is broken down to pyrimidine in the course of its metabolism in leukocytes. After intravenous administration of thiamine to normal persons a significant increase in the concentration of pyrimidine in the blood cells and the urine occurs. However, administration of thiamine to persons with

20. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract: I. Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastro-Intestinal Tract, J. Clin. Investigation **20**:749-764 (Nov.) 1941.

21. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Gastrointestinal Cancer: III. The Hepatic Concentrations of Vitamin A, Proc. Soc. Exper. Biol. & Med. **48**:488-492 (Nov.) 1941.

22. Breese, B. B., Jr.; Watkins, E., and McCord, A. B.: The Absorption of Vitamin A in Tuberculosis, J. A. M. A. **119**:3-4 (May 2) 1942.

23. Haig, C., and Post, J.: Vitamin A Concentration in Rat Liver During Recovery from CCl_4 Cirrhosis, Proc. Soc. Exper. Biol. & Med. **48**:710-714 (Dec.) 1941.

24. Wohl, M. G., and Feldman, J. B.: The Occurrence of Avitaminosis A in Diseases of the Liver, Am. J. Digest. Dis. **8**:464-469 (Dec.) 1941.

25. Haig, C., and Patek, A. J., Jr.: Vitamin A Deficiency in Laennec's Cirrhosis: The Relative Significance of the Plasma Vitamin A and Carotenoid Levels and the Dark Adaptation Time, J. Clin. Investigation **21**:309-317 (May) 1942. Stewart, J. D., and Rourke, G. M.: Vitamin A Content of Plasma and Hepatic Tissue Biopsied at Operation: Effects of Preoperative Therapy in Obstructive Jaundice, Surgery **11**:939-948 (June) 1942. Oldham, Roberts, MacLennan and Schultz.[15a]

26. Ralli, E. P.; Bauman, E., and Roberts, L. B.: The Plasma Levels of Vitamin A After the Ingestion of Standard Doses: Studies in Normal Subjects and Patients with Cirrhosis of the Liver, J. Clin. Investigation **20**:709-713 (Nov.) 1941.

27. Gorham, A. T.; Abels, J. C.; Robins, A. L., and Rhoads, C. P.: The Measurement and Metabolism of Thiamin and of a Pyrimidine Stimulating Yeast Fermentation Found in the Blood Cells and Urine of Normal Individuals, J. Clin. Investigation **21**:161-176 (March) 1942.

leukemia is not followed by any increase in the pyrimidine content of leukocytes, although normal amounts of both thiamine and pyrimidine are excreted in the urine.[28]

Appraisals of methods for measuring thiamine in blood and in urine and a discussion of their possible value in determining the nutritional status of human beings were published in the last year.[29]

Raw cow's milk contains 41 to 48 micrograms of thiamine hydrochloride per hundred cubic centimeters; pasteurization leads to losses of 10 to 20 per cent. Evaporated milk contains 18 to 27 micrograms per hundred cubic centimeters. Early in the lactating period human milk contains much less thiamine than cow's milk.[30] The thiamine content gradually increases until about the twelfth week of the period, after which it remains almost constant.[31] It also has been reported [32] that thiamine is excreted in sweat. A man may lose from 2 to 3 Kg. of weight daily in sweat without visible perspiration and thus may lose a significant amount of thiamine. It was suggested that a person performing hard labor in a high environmental temperature may lose enough thiamine to have serious consequences.

Development of a syndrome simulating Wernicke's disease has been encountered in foxes fed a diet containing raw carp. Further study of the problem revealed that this is due to inactivation of a specific vitamin by a constituent of carp. The substance apparently is not present in the muscle of the carp but in the skin, scales, skeleton, head and viscera. It is destroyed by cooking. Large amounts of thiamine must be mixed with the raw fish to prevent the syndrome, but if the thiamine is given at a time when it will not be mixed with the fish, either in the feed pan or in the gastrointestinal tract, only a small amount is needed to prevent development of the syndrome. The possibility that other dietary constituents may destroy a given vitamin or in some way cause a normally adequate supply of that vitamin to become insufficient demands consideration both in human and in veterinary medicine.[33] Macht and Spencer [34] described interactions between cobra venom and thiamine.

Clinical Studies.—Severe restriction of thiamine is associated with progressive inactivity, apathy, derangement of metabolic processes and loss of weight finally

28. Abels, J. C.; Gorham, A. T.; Craver, L., and Rhoads, C. P.: The Measurement and Metabolism of Thiamin and of a Pyrimidine Stimulating Yeast Fermentation Found in the Blood Cells and Urine of Patients with Leukemia, J. Clin. Investigation **21**:177-189 (March) 1942.

29. Harris, L. J., and Wang, Y. L.: Vitamin Methods: I. An Improved Procedure for Estimating Vitamin B_1 in Foodstuffs and Biological Materials by the Thiochrome Test Including Comparisons with Biological Assays, Biochem. J. **35**:1050-1067, 1941. Egaña, E., and Meiklejohn, A. P.: The Estimation of Thiamine in Urine, J. Biol. Chem. **141**:859-870 (Dec.) 1941. Youmans, J. B.; Patton, E. W., and Sutton, W. R.: The Clinical Significance of Blood Thiamin (Fermentation Method) Values, Tr. A. Am. Physicians **56**:377-383, 1941. Kirch, E. R., and Bergeim, O.: The Chemical Determination of Thiamine, J. Biol. Chem. **143**:575-588 (May) 1942. Stotz, E., and Bessey, O. A.: The Blood Lactate-Pyruvate Relation and Its Use in Experimental Thiamine Deficiency in Pigeons, ibid. **143**:625-631 (May) 1942. Mason, H. L., and Williams, R. D.: The Urinary Excretion of Thiamine as an Index of the Nutritional Level: Assessment of the Value of a Test Dose, J. Clin. Investigation **21**:247-255 (March) 1942.

30. Kendall, N.: Thiamin Content of Various Milks, J. Pediat. **20**:65-73 (Jan.) 1942.

31. Slater, E. C., and Rial, E. J.: The Thiamin (Vitamin B_1) Content of Human Milk, M. J. Australia **1**:3-12 (Jan. 3) 1942.

32. Hardt, L. L., and Still, E. U.: Thiamin in Sweat, Proc. Soc. Exper. Biol. & Med. **48**:704-707 (Dec.) 1941.

33. Green, R. G.; Carlson, W. E., and Evans, C. A.: The Inactivation of Vitamin B_1 in Diets Containing Whole Fish, J. Nutrition **23**:165-174 (Feb.) 1942.

34. Macht, D. I., and Spencer, E. C.: Pharmacological Interactions of Cobra Venom and Thiamine, J. Am. Pharm. A. (Scient. Ed.) **31**:146-150 (May) 1942.

ending in prostration. In all cases of induced deficiency of thiamine mental and physical inefficiency preceded by weeks or months other more objective manifestations. With further studies of this problem Williams and his associates [35] found the optimal intake of thiamine hydrochloride for human beings to be not less than 0.5 mg. or more than 1.0 mg. for each 1,000 calories of a diet providing carbohydrates and fats in conventional proportions.

Low concentrations of thiamine in the blood were encountered frequently in alcoholic addicts who presented acute peripheral neuropathy.[36] Machella and Elsom [37] did not find any essential difference in the percentage of ingested thiamine excreted in the urine of the control subjects and that excreted in the urine of patients with hepatic disease receiving a basal diet. However, when such a diet was supplemented with thiamine, patients with hepatic disease excreted less thiamine than did the controls. These authors suggested that impairment of intestinal absorption may result from hepatic disease.

A critical review of the use of thiamine in the treatment of nerve deafness and tinnitus appeared.[38] The authors did not find any conclusive evidence in favor of the use of this vitamin for this purpose. Thiamine was claimed to be of some value in the treatment of "dry socket" [39] and oral leukoplakia,[40] and its use in eclampsia was suggested.[41]

Observations reported by Smith and Mason [42] failed to provide any grounds for the assumption that the level of intake of thiamine influenced either the intensity of diabetes or the sensitivity to the action of insulin. The relatively mild degree of depression of tolerance for carbohydrate which has been encountered in intact animals and human beings after long periods of deprivation of thiamine appears to represent a disturbance of metabolism unrelated to that involved in diabetes mellitus. Such "false diabetes" is correctable by administration of thiamine; the same is not true of diabetes mellitus. The administration of large doses of vitamin B complex for sixteen weeks to diabetic patients was reported not to have had any discernible effect on the severity of the disease,[43] and thiamine has been found not to be of any help in treatment of protracted diabetic coma or insulin shock.[44]

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35. Williams, R. D.; Mason, H. L.; Smith, B. F., and Wilder, R. M.: Induced Thiamine (Vitamin B_1) Deficiency and the Thiamine Requirement of Man: Further Observations, Arch. Int. Med. **69**:721-738 (May) 1942.

36. Goodhart, R.: The Thiamin Content of Human Blood and Urine as Determined by the Fermentation Method, J. Clin. Investigation **20**:625-630 (Nov.) 1941.

37. Machella, T. E., and Elsom, K. O.: Studies of the B Vitamins in the Human Subject: Urinary Excretion of Ingested Thiamine in Patients with Chronic Hepatic Disease, Am. J. M. Sc. **202**:512-516 (Oct.) 1941.

38. Shambaugh, G. E., Jr., and Jennes, M. L.: Therapy of Nerve Deafness and Tinnitus Aurium: Use of Large Doses of Thiamine Hydrochloride and Evaluation of Results, with a Source of Possible Error in Interpretation of Improvement, Arch. Otolaryng. **35**:513-522 (April) 1942.

39. Osterloh, J. P.: Thiamine Hydrochloride in the Treatment of "Dry Socket," J. Am. Dent. A. **29**:1445-1446 (Aug. 1) 1942.

40. Abels, J. C.; Rekers, P. E.; Martin, H., and Rhoads, C. P.: The Relationship Between Dietary Deficiency and the Occurrence of Papillary Atrophy of the Tongue and Oral Leukoplakia, Cancer Research **2**:381-393 (June) 1942.

41. Nixon, W. C. W.; Wright, M. D., and Fieller, E. C.: Vitamin B_1 in the Urine and Placenta in Toxaemia of Pregnancy, Brit. M. J. **1**:605-607 (May 16) 1942.

42. Smith, K. A., and Mason, H. L.: Thiamin and Diabetes Mellitus, Proc. Staff Meet., Mayo Clin. **15**:529-532 (Aug. 21) 1940.

43. Robson, G. B.; Cutting, W. C., and Gray, H.: Effect of the Vitamin B Complex in Diabetes Mellitus, J. Clin. Endocrinol. **2**:262-263 (April) 1942.

44. Somerfeld-Ziskind, E.; Ziskind, E.; Dalton, L., and Buck, V.: Vitamin B_1 Not Helpful in Protracted Insulin Shock, Am. J. M. Sc. **203**:110-114 (Jan.) 1942.

A review of the literature on untoward reactions to thiamine hydrochloride was published recently, and 2 more cases of sensitivity to this compound were added to the literature.[45] It is interesting that in these cases the patients were able to tolerate the vitamin when it was administered orally and yet showed definite allergic reactions after parenteral administration. It has been suggested that cutaneous testing of patients about to receive thiamine hydrochloride parenterally be made as a precautionary measure. However, the report by Kalz [46] did not fully confirm this advice. Kalz injected thiamine hydrochloride intradermally into 30 patients and a histamine-like reaction consisting of an urticarial wheal with a surrounding erythematous area from 3 to 6 cm. in diameter occurred in all. It was suggested that thiamine hydrochloride is an obligate wheal-producing substance and therefore positive intradermal tests with it are not conclusive proof of an individual subject's sensitivity.

NIACIN

Chemistry and Physiology.—The Food and Nutrition Board of the National Research Council recently selected niacin and niacin amide as suitable synonyms for nicotinic acid and nicotinic acid amide. The Council on Foods and Nutrition of the American Medical Association accepted these synonyms.[47]

Trigonelline and nicotinuric acid are the two known end products of the metabolism of nicotinic acid encountered in urine of human beings. In an excellent study by Sarett and his associates [48] 10 mg. of known niacin derivative was found in the urine daily, regardless of diet. After oral administration of a 200 mg. dose of niacin 25 to 90 mg. could be accounted for by the increase of 55 to 84 per cent in urinary trigonelline and of 16 to 45 per cent in urinary nicotinuric acid. Interestingly enough, trigonelline is not utilized by human beings when taken orally and is excreted almost completely without change. About 60 per cent of nicotinuric acid ingested is excreted unchanged and without an accompanying increase in trigonelline.

Further studies on the metabolism of niacin have been made by Najjar and associates,[49] who described the presence in the urine of certain fluorescent substances which varied in a characteristic way in pellagra. One of these, designated "F_1," occurred in relatively small amounts in normal urine but in large quantities in the urine of pellagrins. The second substance, designated "F_2," present in normal urine was increased in amount when niacin was administered. The second substance was not encountered usually in the urine of pellagrins but appeared after administration of niacin. The urinary excretion of both substances was followed in dogs with experimental niacin deficiency, and observations on these animals are in agreement with those made on human beings with pellagra. Acute niacin deficiency is followed by a disappearance of excretion of the second substance and an increase in excretion of the first substance; as the disease becomes chronic, even the excretion of the first substance tends to fall.

45. Eisenstadt, W. S.: Hypersensitivity to Thiamine Hydrochloride, Minnesota Med. **25**: 861-863 (Nov.) 1942.

46. Kalz, F.: Thiamine Hydrochloride—An Obligate Wheal Producing Agent, J. Invest. Dermat. **5**:135-137 (June) 1942.

47. Niacin and Nicotinic Acid, editorial, J. A. M. A. **118**:823 (March 7) 1942.

48. Sarett, H. P.; Huff, J. W., and Perlzweig, W. A.: Studies in Nicotinic Acid Metabolism: I. The Fate of Nicotinic Acid in Man, J. Nutrition **23**:23-24 (Jan.) 1942.

49. Najjar, V. A.; Stein, H. J.; Holt, L. E., Jr., and Kabler, C. V.: The Excretion of Specific Fluorescent Substances in the Urine in Experimental Nicotinic Acid Deficiency, J. Clin. Investigation **21**:263-267 (May) 1942.

Further studies on the distribution of niacin in foods were reported.[50] All animal tissue contains niacin, but the liver and the kidney are the richest sources.[51] Cooking and commercial processing apparently cause some loss of the vitamin. New methods for measuring niacin in animal tissues and blood were reported,[52] and a method for determining niacin deficiency in human beings was described.[53]

Clinical Use.—Manson-Bahr [54] advanced the hypothesis that the syndrome of sprue is mainly the result of nonabsorption or destruction of factors of vitamin B_2 complex in the small intestine. He administered orally 150 mg. of niacin each day for fourteen days of each month for six months. At the end of this time the patient was improved markedly. Intensive parenteral liver therapy was continued, however, in conjunction with this specific treatment.

It is well known that niacin has a vasodilating action and because of this fact its use in the treatment of asthma has been suggested.[55] Twenty-one patients in asthmatic paroxysms received intravenously 0.1 Gm. of niacin, and of these 21, 11 had relief within three to five minutes after the injection. The relief seemed to coincide with the appearance of a flush, which is a common reaction following parenteral use of niacin. The duration of the relief lasted from a few to fifteen hours. Nine patients were given oral doses of 0.2 Gm. before each meal. Five of these 9 patients were benefited.

RIBOFLAVIN

No new important clinical advances in knowledge of this vitamin have come to our attention. Machella [56] reported healing of cheilosis in 9 of 13 patients receiving pyridoxine. The remaining few patients failed to respond either to riboflavin or to pyridoxine, but 1 of them responded to nicotinic acid. Other investigators also have noted that cheilosis in some cases heals only when the entire vitamin B complex in the form of liver extract and brewers' yeast is supplied. These observations indicate that cheilosis is not necessarily a manifestation of riboflavin deficiency alone.

New laboratory methods for measuring riboflavin deficiency in human beings appeared within the year.[57]

PYRIDOXINE

The controversy concerning the effectiveness of pyridoxine in the treatment of neuromuscular diseases is lessening. The results of treatment are not encouraging.

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50. Teply, L. J.; Strong, F. M., and Elvehjem, C. A.: The Distribution of Nicotinic Acid in Foods, J. Nutrition **23**:417-423 (April) 1942.

51. McIntire, J. M.; Waisman, H. A.; Henderson, L. M., and Elvehjem, C. A.: Nicotinic Acid Content of Meat and Meat Products, J. Nutrition **22**:535-540 (Nov.) 1941.

52. Giri, K. V., and Naganna, B.: An Adsorption Method for the Estimation of Nicotinic Acid Content of Animal Tissues and Blood, Indian J. M. Research **29**:585-590 (July) 1941. Jones, W. S.: Photoelectric Determination of Nicotinic Acid, J. Am. Pharm. A. (Scient. Ed.) **30**:272-275 (Oct.) 1941.

53. Perlzweig, W. A.; Sarett, H. P., and Margolis, L. H.: Studies in Nicotinic Acid Metabolism: V. A Test for Nicotinic Acid Deficiency in Man, J. A. M. A. **118**:28-30 (Jan. 3) 1942.

54. Manson-Bahr, P.: The Treatment of Sprue with Vitamin B_2 and Its Bearing upon the Aetiology of This Disease, Tr. Roy. Soc. Trop. Med. & Hyg. **34**:347-372 (March) 1941.

55. Maisel, F. E., and Somkin, E.: Treatment of Asthmatic Paroxysms with Nicotinic Acid: Preliminary Report, J. Allergy **13**:397-403 (May) 1942.

56. Machella, T. E.: Studies of the B Vitamins in Human Subjects: III. The Response of Cheilosis to Vitamin Therapy, Am. J. M. Sc. **203**:114-120 (Jan.) 1942.

57. Jones, W. S., and Christensen, W. G.: Fluorophotometric Determinations of Riboflavin, J. Am. Pharm. A. (Scient. Ed.) **30**:270-272 (Oct.) 1941. Najjar, V. A.: The Fluorometric Determination of Riboflavin in Urine and Other Biological Fluids, J. Biol. Chem. **141**:355-364 (Nov.) 1941. Najjar, V. A., and Holt, L. E., Jr.: A Riboflavin Excretion Test as a Measure of Riboflavin Deficiency in Man, Bull. Johns Hopkins Hosp. **69**:476-481 (Nov.) 1941.

Meller [58] reported that in 4 cases of postencephalitic paralysis agitans improvement did not occur after treatment with pyridoxine but in 6 cases of idiopathic paralysis agitans this type of therapy decreased pain and rigidity and increased general well-being. Keith [59] did not note any benefit in the treatment with pyridoxine of pseudohypertrophic muscular dystrophy among children.

Jolliffe and his associates [60] have reported some success in treatment of persistent postadolescent acne vulgaris. From 50 to 250 mg. of pyridoxine was given orally each day in divided doses. Of 37 patients, 9 were cleared of the disease and 19 were improved. Of the control group of 35 patients given starch and sugar tablets, 7 were improved.

PANTOTHENIC ACID

It has been suggested that pantothenic acid may be involved in the regulation of water metabolism,[61] and recent experimental data suggest that this substance is required for maintaining the integrity of the adrenal cortex.[62] It may be of some interest to know that honey contains pantothenic acid [63] and that royal jelly, a secretion of the pharyngeal glands of worker honey bees, is reported to be the richest known source of this substance. On a dry basis royal jelly contains an average of 511 micrograms of pantothenic acid per gram; this is between two and a half and six times as much as is present in yeast or liver.[64]

A few clinical studies of pantothenic acid have appeared. Wright and Wright [65] reported on the urinary excretion of pantothenic acid of 29 normal persons. The mean daily excretion was 3.42 mg. in twenty-four hours. These results compare favorably with those reported by Pelzar and Porter, mentioned in last year's review. The daily urinary excretion of pantothenic acid by patients with pernicious anemia does not indicate impairment of absorption of this compound.[66] It is known that in rats with experimentally produced hyperthyroidism administration of thiamine will arrest loss of weight but that lost weight is not regained until a rich source of the vitamin B complex, such as yeast, is added to the diet. Drill and Overman [67] reported that pyridoxine and calcium pantothenate can effectively replace yeast in such experiments and that, like thiamine, these substances are required in greater amounts during hyperthryroidism.

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58. Meller, C. L.: Ten Cases of Paralysis Agitans Treated with Vitamin B_6, Minnesota Med. **25**:22-24 (Jan.) 1942.

59. Keith, H. M.: Vitamin B_6 (Pyridoxine Hydrochloride) in the Treatment of Pseudohypertrophic Muscular Dystrophy Among Children, J. Pediat. **20**:200-207 (Feb.) 1942.

60. Jolliffe, N.; Rosenblum, L. A., and Sawhill, J.: The Effects of Pyridoxine (Vitamin B_6) on Persistent Adolescent Acne, J. Invest. Dermat. **5**:143-148 (June) 1942.

61. Figge, F. H. J., and Atkinson, W. B.: Relation of Water Metabolism to Porphyrin Incrustations in Pantothenic Acid–Deficient Rats, Proc. Soc. Exper. Biol. & Med. **48**:112-114 (Oct.) 1941.

62. Supplee, G. C.; Bender, R. C., and Kahlenberg, O. J.: Interrelated Vitamin Requirements: Kidney Damage, Adrenal Hemorrhage and Cardiac Failure Correlated with Inadequacy of Pantothenic Acid, Endocrinology **30**:355-364 (March) 1942.

63. Haydak, M. H.; Palmer, L. S.; Tanquary, M. C., and Vivino, A. E.: Vitamin Content of Honeys, J. Nutrition **23**:581-588 (June) 1942.

64. Pearson, P. B., and Burgin, C. J.: The Pantothenic Acid Content of Royal Jelly, Proc. Soc. Exper. Biol. & Med. **48**:415-417 (Nov.) 1941.

65. Wright, L. D., and Wright, E. Q.: Urinary Excretion of Pantothenic Acid by Normal Individuals, Proc. Soc. Exper. Biol. & Med. **49**:80-81 (Jan.) 1942.

66. Meyer, C. E.; Burton, I. F., and Sturgis, C. C.: Pantothenic Acid Absorption in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **49**:363-365 (March) 1942.

67. Drill, V. A., and Overman, R.: Increased Requirements of Pantothenic Acid and Vitamin B_6 During Experimental Hyperthyroidism, Am. J. Physiol. **135**:474-477 (Jan.) 1942.

BIOTIN

This relative newcomer to the field of nutrition was considered briefly in last year's review. Now, for the first time, induced biotin deficiency has been produced in human beings.[68] Many investigators have noticed that the inclusion of large amounts of egg white in special experimental diets will produce definite nutritional disease in animals. This disease is commonly called "egg white injury" and is characterized chiefly by the appearance of a rather severe, general eczematous dermatitis involving the eyelids and the lips. Egg white injury can be prevented or cured by administration of biotin. It is due to an induced biotin deficiency caused by the binding of dietary biotin by a protein fraction of raw egg white (avidin), thereby preventing the absorption of this vitamin from the intestinal tract.[69]

Sydenstricker and his associates maintained 4 volunteers on a diet poor in all vitamins of the B group (except riboflavin, supplied by egg white); at least 30 per cent of the total caloric intake was supplied by desiccated egg white. During the third and the fourth week all 4 of these subjects had a fine scaly dermatitis, which disappeared spontaneously and which did not itch. During the seventh and the eighth week all 4 patients exhibited a grayish pallor of the skin, apparently owing to peripheral vasoconstriction, and the 3 white volunteers had definite atrophy of the lingual papillae, which the Negro volunteer did not have until the fourteenth week. By the ninth and the tenth week dryness of the skin of the extremities, well defined reticulation and tendency again to fine, grainy desquamation were present in all cases. Ocular or genital lesions were not observed. After the fifth week depression, muscular pain, anorexia and precordial pain developed. All of these symptoms and signs were cured rapidly by parenteral administration of a biotin concentrate in doses representing 150 to 300 micrograms of biotin per day.

ASCORBIC ACID

Chemical and Physiologic Properties.—The level of ascorbic acid in the blood of human beings is not significantly affected by elevating the body temperature to 104 F. for periods as long as four hours.[70] In the guinea pig the sedative effect of soluble pentobarbital is greatly prolonged if the animal has been kept for periods of thirty-three days on a diet deficient in ascorbic acid. This prolongation of sedative effect can promptly be brought to normal by addition of ascorbic acid to the diet. Deficiency of ascorbic acid, however, had no such effect on the metabolism of pentothal sodium.[71] An interesting study by Rothman[72] suggested that the influence of ascorbic acid on oxidation of tyrosine by ultraviolet irradiation in vitro is threefold: 1. It markedly furthers formation of dihydroxyphenylalanine

68. Sydenstricker, V. P.; Singal, S. A.; Briggs, A. P.; DeVaughn, N. M., and Isbell, H.: Observations on the "Egg White Injury" in Man, J. A. M. A. **118**:1199-1120 (April 4) 1942.

69. Eakin, R. E.; McKinley, W. A., and Williams, R. J.: Egg-White Injury in Chicks and Its Relationship to a Deficiency of Vitamin H (Biotin), Science **92**:224-225 (Sept. 6) 1940. Eakin, R. E.; Snell, E. E., and Williams, R. J.: A Constituent of Raw Egg White Capable of Inactivating Biotin in Vitro, J. Biol. Chem. **136**:801-802 (Dec.) 1940. György, P.; Rose, C. S.; Eakin, R. E.; Snell, E. E., and Williams, R. J.: Egg-White Injury as the Result of Nonabsorption or Inactivation of Biotin, Science **93**:477-478 (May 16) 1941.

70. Osborne, S. L., and Farmer, C. J.: Influence of Hyperpyrexia on Ascorbic Acid Concentration in the Blood, Proc. Soc. Exper. Biol. & Med. **49**:575-578 (April) 1942.

71. Richards, R. K.; Kueter, K., and Klatt, T. J.: Effect of Vitamin C Deficiency on Action of Different Types of Barbiturates, Proc. Soc. Exper. Biol. & Med. **48**:403-409 (Nov.) 1941.

72. Rothman, S.: In Vitro Studies on Pigmentation: II. Influence of Ascorbic Acid on Oxidation of Tyrosine by Ultraviolet Irradiation, J. Invest. Dermat. **5**:67-74 (April) 1942.

(dopa). 2. Further oxidation of this compound is prevented by hydrogen acceptance of ascorbic acid. 3. Melanin is transformed by ascorbic acid into less deeply colored products.

Several new methods for measuring ascorbic acid were reported and criticized.[73]

Clinical Use.—An excellent and complete summary of the metabolism of ascorbic acid in adult scurvy has been published within the year,[74] and a good review of the subject of scurvy in children also was reported, together with the presentation of 15 new cases encountered in children less than 12 years of age.[75] Some authors have maintained that the hemorrhagic features of scurvy are due to a deficiency of vitamin P. In an attempt to settle this question Cameron and Mills[76] gave vitamin P but not ascorbic acid to a patient who had classic scurvy. The hemorrhagic features disappeared promptly, although other features of the disease were unaffected until ascorbic acid was added.

The ascorbic acid requirements of premature infants[77] and school children[78] have been reported, and it has been shown rather definitely that children who receive 3 ounces (90 cc.) or more of orange juice daily or an equivalent amount of ascorbic acid in citrus fruits and tomatoes maintain a liberal level of ascorbic acid in the plasma.[79]

There seems to be little doubt that ascorbic acid is of great importance in the healing of wounds, and during the past year further research in this direction has added greatly to present knowledge. Lund and Crandon[80] reported on a study of 58 patients who underwent operations on the biliary tract. In patients in whom the intake of ascorbic acid was poor or the level of ascorbic acid in the plasma was low preoperatively or both, hernia developed postoperatively more often than in those patients in whom the supply of ascorbic acid was good preoperatively. On the experimental side of this problem Bartlett and his group[81] presented some interesting data. These authors studied the effect of ascorbic acid on healing of wounds by making abdominal incisions on guinea pigs and removing a specimen of tissue for a control biopsy. The wound was allowed to heal for a suitable period, and then the healing tissue was excised. The ascorbic acid content of the excised tissues was then measured. Animals on a scorbutigenic diet did not show any essential increase in ascorbic acid in the healing tissue over that in control specimens and only slightly lowered values in the remainder of the abdominal wall. However,

73. Wiehl, D. G., and Kantorovitz, M.: Medical Evaluation of Nutritional Status: XI. An Analysis of Sources of Errors in the Photelometric Macromethod of Determining Ascorbic Acid in Plasma, Milbank Memorial Fund Quart. **20**:178-206 (April) 1942. Harris, L. J.: Critique of the Saturation Method for Determining Vitamin-C Levels, Lancet **1**:644-646 (May 30) 1942.

74. Ralli, E. P., and Sherry, S.: Adult Scurvy and the Metabolism of Vitamin C, Medicine **20**:251-340 (Sept.) 1941.

75. Moise, D. D.: Scurvy in Children, North Carolina M. J. **3**:290-295 (June) 1942.

76. Cameron, D. G., and Mills, E. S.: Scurvy in Montreal, Canad. M. A. J. **46**:548-550 (June) 1942.

77. Dann, M.: The Influence of Diet on the Ascorbic Acid Requirement of Premature Infants, J. Clin. Investigation **21**:139-144 (March) 1942.

78. Harris, L. J.: Vitamin-C Levels of School-Children and Students in War-Time, Lancet **1**:642-644 (May 30) 1942.

79. Bessey, O. A., and White, R. L.: The Ascorbic Acid Requirement of Children, J. Nutrition **23**:195-204 (Feb.) 1942.

80. Lund, C. C., and Crandon, J. H.: Ascorbic Acid and Human Wound Healing, Ann. Surg. **114**:776-790 (Oct.) 1941.

81. Bartlett, M. K.; Jones, C. M., and Ryan, A. E.: Vitamin C and Wound Healing: I. Experimental Wounds in Guinea Pigs, New England J. Med. **226**:469-473 (March 19) 1942.

when the supply of ascorbic acid was high, a striking increase in the ascorbic acid content of healing tissue over that of the control specimen of tissue was demonstrated. In addition, the tensile strength of wounds in which ascorbic acid content was high was much greater than that of those in which it was low. In studies of wounds in human beings this group of investigators [82] found that a sufficient depletion of ascorbic acid produces a decreased ascorbic acid content and tensile strength of healing wounds in the skin and in fascia. However, before these changes appear a fasting level of ascorbic acid of less than 0.2 mg. per hundred cubic centimeters of plasma must be reached. Others [83] have reported that increasing the dose of ascorbic acid above the normal daily requirement does not result in greater than normal development of tensile strength in wounds and that addition of vitamin P to the diet does not improve the healing process. Deficiency of the vitamin B complex apparently has little effect in healing of wounds in rats.[84] As was stated in an editorial in *The Journal of the American Medical Association*,[85] these observations suggest that under normal conditions of intake and absorption of food the tissues of the average person contain sufficient ascorbic acid to insure normal healing of wounds. The remaining problem is that of demonstrating which person will require supplementary ascorbic acid therapy preoperatively and postoperatively.

The interesting relation of ascorbic acid to arsenical therapy in human beings has continued to receive attention. Of 38 patients who gave strongly positive reactions to patch tests with a 30 per cent solution of neoarsphenamine, only 32 had positive reactions if ascorbic acid was added to the neoarsphenamine.[86] Studies of the plasma levels of ascorbic acid in these patients indicated that such levels do not exert as great an effect in preventing cutaneous reactions to patch tests as the local application of ascorbic acid does. It was suggested that patch tests be performed with 30 per cent neoarsphenamine plus 10 per cent ascorbic acid and that patients who react positively to this test most likely will not be able to tolerate neoarsphenamine. Similar studies have been reported by Abt.[87]

VITAMIN D

An excellent summary of the relation of vitamin D to ossification appeared,[88] and a method for estimation of vitamin D in blood serum was reported.[89]

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82. Bartlett, M. K.; Jones, C. M., and Ryan, A. E.: Vitamin C and Wound Healing: II. Ascorbic Acid Content and Tensile Strength of Healing Wounds in Human Beings, New England J. Med. **226**:474-481 (March 19) 1942.

83. Hartzell, J. B., and Stone, W. E.: The Relationship of the Concentration of Ascorbic Acid of the Blood to the Tensile Strength of Wounds in Animals, Surg., Gynec. & Obst. **75**:1-7 (July) 1942.

84. Holden, J. C., and Crile, G., Jr.: Influence of Vitamin B Complex Deficiency and Partial Starvation on Wound Healing: Experimental Research with Rats, Arch. Surg. **44**: 1106-1110 (June) 1942.

85. Vitamin C and Wound Healing, editorial, J. A. M. A. **119**:564-565 (June 13) 1942.

86. Bundeson, H. N.; Aron, H. C. S.; Greenebaum, R. S.; Farmer, C. J., and Abt, A. F.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy: I. Ascorbic Acid as a Preventive of Reactions of Human Skin to Neoarsphenamine, J. A. M. A. **117**:1692-1695 (Nov. 15) 1941.

87. Abt, A. F.: The Human Skin as an Indicator of the Detoxifying Action of Vitamin C (Ascorbic Acid) in Reactions Due to Arsenicals Used in Antisyphilitic Therapy, U. S. Nav. M. Bull. **40**:291-303 (April) 1942.

88. McGowan, J. P.: On Ossification and Vitamin D Action, Edinburgh M. J. **49**:190-199 (March) 1942.

89. Warkany, J.; Guest, G. M., and Grabill, F. J.: Estimation of Vitamin D in Blood Serum: Vitamin D in Human Serum During and After Periods of Ingestion of Large Doses of Vitamin D, J. Lab. & Clin. Med. **27**:557-565 (Jan.) 1942.

For many years it has been recognized that vitamin D and the irradiated sterol concentrates may produce reactions. Nausea, vomiting, anorexia, abdominal pain, diarrhea, headache and muscular weakness are the symptoms which usually accompany this reaction. Tumulty and Howard[90] reported 2 cases in which a preparation containing vitamin D was administered in large doses, with accompanying prolonged hypercalcemia and persistent impairment of renal function, as measured by inability to concentrate urine normally.

VITAMIN E

Chemistry and Physiology.—It has been suggested[91] and adopted[92] that synthetic racemic tocopherol (tocopheryl) acetate be made the international standard for vitamin E. The international unit is the vitamin E activity of 1.0 mg. of the standard preparation (racemic tocopherol acetate in olive oil; 1.0 Gm. contains 10 mg. of synthetic racemic tocopherol acetate). The quantity represents the average amount which prevents resorption gestation in rats deprived of vitamin E when the substance is administered orally.

A new photoelectric method for determination of alpha tocopherol in human serum was reported within the last year.[93]

Clinical Application.—The hope of success of vitamin E in the treatment of various neuromuscular diseases of human beings has faded rapidly during the past year. A large number of patients with multiple sclerosis, progressive muscular atrophy, muscular dystrophy, amyotrophic lateral sclerosis and other diseases have had adequate treatment with natural and synthetic preparations of vitamin E. The results from such treatment have been most discouraging.[94] Whether further experimental[95] and clinical[96] trials are warranted must be left to the decision of the individual physician. Claims[97] have continued to be made that vitamin E is of value in treatment of fibrositis, but the subject needs further clinical investigation.

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90. Tumulty, P. A., and Howard, J. E.: Irradiated Ergosterol Poisoning: Report of Two Cases, J. A. M. A. **119**:233-236 (May 16) 1942.

91. Hume, E. M.: Standardization of Vitamin E, Nature, London **148**:472-473 (Oct. 18) 1941.

92. Memorandum on the International Standard for Vitamin E, Department of Biological Standards, National Institute for Medical Research, Hampstead, London, Bull. Health Organ., League of Nations **9**:443-446, 1940-1941.

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94. Meller, R. L.: An Evaluation of Vitamin E in the Treatment of Multiple Sclerosis and the Progressive Muscular Atrophies, Journal-Lancet **61**:471-478 (Dec.) 1941. DeJong, R. N.: Vitamin E and Alpha Tocopherol Therapy of Neuromuscular and Muscular Disorders, Arch. Neurol. & Psychiat. **46**:1068-1073 (Dec.) 1941. Harvey, R. W., and Hume, P. B.: Vitamin E and Nervous Diseases, California & West. Med. **55**:293-295 (Dec.) 1941. Merwarth, H. R.: Synthetic Vitamin E in the Treatment of Amyotrophic Lateral Sclerosis and Related Disorders: Report of Six Cases, Dis. Nerv. System **2**:325-329 (Oct.) 1941. Viets, H. R.; Trowbridge, E. H., Jr., and Gundersen, T. E.: The Treatment of Certain Muscular Atrophies with Vitamin E, with a Note on Diagnosis and the Electromyograms, Am. J. M. Sc. **203**:558-556 (April) 1942. Lubin, A. J.: Use of Alpha Tocopherol in the Treatment of Neuromuscular Disorders, Arch. Int. Med. **69**:836-855 (May) 1942. Hawke, W. A.: Vitamin Therapy of Muscular Dystrophy, Canad. M. A. J. **47**:153-155 (Aug.) 1942.

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VITAMIN K

Physiology and Chemistry.—This year little can be added to the excellent consideration of the chemistry of vitamin K by Fieser,[98] mentioned in last year's review. New calorimetric procedures for accurate chemical determinations of K vitamins have been described,[99] and they give hope that even simpler quantitative procedures soon will be available. Scudi [100] reported the interesting observation that when menadione is added to whole unlaked blood, it causes marked formation of methemoglobin and that the drug is converted rapidly to some other substance. However, under comparable conditions vitamin K_1 does not produce methemoglobin.

An excellent summary of the role of vitamin K in coagulation of blood appeared,[101] and Rhoads and his group [102] reviewed the work on experimental hypoprothrombinemia. Tocantins [103] reported that exposure of citrated or oxalated plasma to an air current is followed by rapid diminution in its prothrombin activity. This phenomenon is corrected by addition of carbon dioxide but is not affected by addition of oxygen. The author suggested that asphyxia or hyperventilation may lead to significant fluctuation in the level of prothrombin in the blood.

While attempting to produce experimental hemorrhagic disease in newborn animals Moore and his associates [104] observed that rabbits which received a diet deficient in vitamin K for forty days and then mated invariably aborted from the tenth to the fourteenth day of pregnancy. Necropsy revealed retroplacental hemorrhage. It is interesting that the level of prothrombin in the plasma did not fall to so-called "critical levels" and that the only point of hemorrhage was in the placenta. It is suggested that the placenta is unusually susceptible to deprivation of vitamin K.

The possibility that pancreatic disease also may be accompanied by deficiency of prothrombin is suggested by the report that pancreatic achylia and pancreatectomy, at least in the cat, are followed by reduction in the level of prothrombin in the blood.[105]

Another interesting contribution on the physiology of vitamin K was made by Overman and his associates.[106] These authors observed that when the rat ingests 3,3′-methylenebis-(4-hydroxycoumarin) need for vitamin K appears to be increased. Vitamin K was found to counteract hypoprothrombinemia induced by the anticoagulant whether given before the anticoagulant, with it or twelve hours later.

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Clinical Use.—Previous reports showing the value of vitamin K in preventing hemorrhage associated with deficiency of prothrombin in the circulating blood continue to be confirmed. A few new and interesting clinical developments have been reported. Rhoads and Fitz-Hugh [107] studied the case of a white youth aged 18 who had had episodes of hemorrhagic diathesis throughout most of his life. This diathesis was due apparently to an idiopathic hypoprothrombinemia and an associated abnormality of the fibrinogen. Rhoads and Fitz-Hugh were unable to correct the deficiency of prothrombin by administration of synthetic substances with vitamin K activity. Another interesting case of hypoprothrombinemia was reported by Coller and Farris.[108] Within three days after a massive gastric hemorrhage the patient received 3,200 cc. of blood and, in addition, 7,500 cc. of fluid intravenously. Two days later a marked deficiency of prothrombin was found which was nearly completely corrected within twenty-four hours by administration of vitamin K. The patient had taken a normal diet and did not have any abnormality of the biliary tract or the liver. At necropsy a bleeding gastric ulcer was found. The authors suggested that sufficient depletion of prothrombin reserve could result from repeated dilution of the blood with solutions of sodium chloride and dextrose. This possibility deserves further investigation. These authors also confirmed the observation that deficiency of prothrombin can develop after simple, continued aspiration of bile from the gastrointestinal tract with suction apparatus.[109]

In contrast to previous reports, Levy [110] observed that 32 per cent of the patients with pulmonary tuberculosis studied by him had a more or less marked degree of prothrombin deficiency. It is interesting that 87 per cent of these patients had parenchymal hepatic damage. Levy also found that vitamin K had a beneficial effect on the treatment and prevention of hemorrhage in tuberculosis.

Vitamin K continues to be widely and successfully employed in treatment and prevention of certain hemorrhagic diseases of newborn infants. Hellman and Shettles [111] have advocated that 2 mg. of menadione, or any preparation with similar activity, be given to pregnant women daily for at least two weeks prior to onset of labor. They stated that 20 to 40 per cent of the 128,000 infants who do not survive each year show some evidence of cerebral hemorrhage. It is hoped that the plan they suggested may result in the saving of many of these lives.

Ross and Malloy [112] reported on a group of newborn infants suffering from asphyxia who had a marked deficiency of prothrombin and suggested that anoxemia may be a factor in production of deficiency of prothrombin. Induced anoxemia in newborn chicks resulted in similar findings. The observations are supported by the experimental work of Tocantins, mentioned previously.[102]

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The percutaneous use of vitamin K has again been advocated,[113] but other investigators[114] have found this method of administration unsatisfactory because of the ensuing dermatitis in more than 50 per cent of the cases studied.

Seligman and his associates[115] have described a method of preparing pure vitamin K in colloidal suspension for intraveous administration. A single 10 mg. dose of this compound has a much longer effect than that of an equivalent dose of menadione. This compound administered in this dose to a patient with an elevated prothrombin time resulted in a normal prothrombin time for twenty-six days.

The old problem of attempting to evaluate the degree of hepatic damage by the response of prothrombin to administration of vitamin K has received considerable attention. Kark and Souter,[116] in an effort to interpret better this test of hepatic function, have subdivided the response of prothrombin to vitamin K into five subdivisions. In the first group the response to vitamin K is prompt, and it was assumed that in these instances no gross hepatic damage exists. In the second group the level of prothrombin in the blood rises somewhat but remains fixed at a subnormal level despite treatment with vitamin K; in this group the hepatic damage is of a moderate and variable degree. In the third group the level of prothrombin in the blood gradually rises as clinical improvement becomes apparent. In the fourth group the level of prothrombin fluctuates in a subnormal zone which is above the threshold for hemorrhage, irrespective of therapy. Patients in this group have chronic hepatic disease of long standing, usually unassociated with jaundice. In the fifth group the level of prothrombin decreases in spite of therapy or remains below the level for hemorrhage. In this group hepatic damage is severe and widespread.

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Book Reviews

Intestinal Obstructions: A Physiological and Clinical Consideration with Emphasis on Therapy, Including Description of Operative Procedures. By O. H. Wangensteen. Second edition. Price, $7. Pp. 484. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

This is an excellent treatise on the important and serious clinical problem of intestinal obstruction. From the preface through the last page of the last chapter, which deals with obstructions owing to vascular causes, the book is full of practical suggestions regarding the manner in which intestinal obstruction disturbs the economy of the body and regarding diagnostic, as well as therapeutic, procedures for this most devastating human ailment.

The author wisely has divided the subject into four parts as follows: physiologic and clinical considerations; general diagnosis; therapeutic considerations, and special obstructions.

Part 1, on physiologic and clinical considerations of intestinal obstruction, consists of one chapter of 60 pages which is divided into seven parts. In this portion of the book the author deals with the systemic effects, character and source of distention and its manifestations on the intestinal wall. Absorption in the presence of obstruction, the significance of the factor of loss of blood in strangulating obstructions and the nature of the toxemia associated with obstruction are explained.

Although it is stated that no direct and unequivocal answer has been obtained to the question of lethal factors in obstruction, the author's opinion seems to be that apart from the loss of fluids and electrolytes, which is of serious consequence, the chief effects of obstruction are mechanical and concern intraenteric pressure as related to absorption and the viability of the intestinal wall. When the viability of the wall has become impaired, then permeation by bacteria and other deadly agents occurs, but this is a secondary rather than a primary phenomenon.

Part 2, on general diagnostic considerations, is 41 pages long and is divided into two chapters; in one diagnostic methods for acute abdominal disorders and in the other the recognition of obstruction are considered. In the latter chapter the author explains the methods of determining that obstruction exists, of localizing the obstructing lesion and of determining whether obstruction is partial or complete and finally the mechanism of the obstruction.

In part 3 seven chapters (chapters 4 to 10 inclusive), 140 pages, are devoted to the management of acute intestinal obstruction. In chapter 4 the author considers guiding principles in the treatment of acute abdominal lesions; in chapter 5 the important supportive measures are listed, namely, administration of physiologic solution of sodium chloride, transfusion of blood and plasma and inhalation of oxygen in high concentrations, and in chapter 6 the technic of decompression by application of suction through duodenal tubes is outlined. Indications for this conservative method of treatment and shortcomings of suction are explained. In chapter 7 operative procedures, preoperative preparation and choice of anesthetic are outlined. Chapter 8 is devoted to closed aseptic resection. Postoperative treatment is considered in chapter 9 and mortality in chapter 10.

In part 4, on the special obstructions, fifteen chapters are devoted to a discussion of obstruction due to congenital atresia of the intestine; the imperforate anus; tumors and strictures of the intestinal wall; obturation; fecal obstruction, as occurs in megacolon; compression of the bowel by extrinsic conditions, such as pelvic lesions, adhesions and bands; external hernia; internal hernia; volvulus; intussusception; errors in development of the intestine; inhibition (paralytic) ileus; spastic ileus, and obstruction owing to vascular causes.

Any practitioner of medicine will be proud to have this book in his reference library. Every teacher of medicine should have it available as a textbook, for it contains the most modern information on the subject and sound information for students. More than that, any one reading it will find that it is written in an interesting, almost fascinating manner.

Publicaciones del centro de investigaciones tisiologicas. Vol. 5. Pp. 388, with 28 illustrations. Buenos Aires: Pabellon "Las Provincias," Hospital Tornu, 1941.

This collection of eleven papers from the Center of Tuberculosis Research, Buenos Aires, Argentina, under the direction of Prof. Roque A. Izzo, testifies to the thoroughly scientific work being carried on in Argentina, as in other South American countries. The influence of the best in German and in French medical thought on this subject is obvious. North American authors are also frequently cited. The summaries in German, French and English will aid the reader who is not familiar with Spanish, in which language the text is written.

The detailed analysis of the results of artificial pneumothorax treatment is one of the best to be found in the world's literature. Prof. Oscar P. Aguilar's discussion of Ranke's secondary tuberculosis is thorough and stimulating. The shorter papers on results of the Jacobeus operation, absorption of ultraviolet light, behavior of lymphocytes to tubercle bacilli in vitro and tuberculin allergy of infants are all of the same high standard.

The Care of the Aged (Geriatrics). By Malford W. Thewlis, M.D. Fourth edition, revised. Price, $7, cloth. Pp. 589, with 50 illustrations. St. Louis: C. V. Mosby Co., 1942.

The disproportionate increase in population in the higher age groups in this country in the past twenty years, which in all likelihood will increase still further, has stimulated much interest in the subject of gerontology and geriatrics by physiologists, pathologists and clinicians.

This work is balanced poorly, mainly because certain features are emphasized unduly, while others are neglected or merely mentioned; furthermore, there is too much repetition. There is a moderately comprehensive bibliography at the end of each chapter.

The reviewer feels that this work falls too far short of its possibilities to encourage students or clinicians to invest in it.

Synopsis of Pathology. By W. A. D. Anderson, M.D., Assistant Professor of Pathology, St. Louis University School of Medicine; Pathologist, St. Mary's Group of Hospitals. Price, $6, cloth, octavo. Pp. 638, with 294 illustrations in the text and 17 colored plates. St. Louis: C. V. Mosby Company, 1942.

The author states that his purpose in compiling this book was "to fill a gap which has existed between the very elementary manuals of pathology and the abundant excellent larger textbooks and reference works." It is the opinion of the reviewer that he has succeeded in large measure in producing "a concise synopsis of pathology in which essentials are included but the broad outlines and patterns of disease are not obscured by a mass of detail."

The illustrations are well chosen and clearly reproduced. A short bibliography is appended to each chapter, and a general index is included. This book should be useful for quick reference by medical and by dental students as well as by clinicians in general practice.

The Food You Eat. By Samuel and Violette Classtone. Price, $2.25. Pp. 277, with 18 illustrations. Norman, Okla.: The University of Oklahoma Press, 1942.

This is the best semipopular book on food and nutrition the reviewer has yet seen. The writers are obviously experts and have a large backlog of solid scientific information to draw on. They write well and make their points with a quiet emphasis which is sufficiently convincing. The flamboyant or evangelistic style used by so many propagandists of nutrition is conspicuously absent. The theoretic part of the subject is covered in such a way as to be intelligible to the average educated reader, and the practical discussion of food and of menus is satisfactory. The book does credit to the university press which produced it.

Carcinoma of the Stomach. By Waltman Walters, M.D.; Howard K. Gray, M.D.; James T. Priestley, M.D., and associates in the Mayo Clinic and the Mayo Foundation. Price, $8.50. Pp. 576, with 178 illustrations on 143 figures, 2 in colors. Philadelphia: W. B. Saunders Company, 1942.

The chief new contribution of this monograph is a statistical analysis of almost 11,000 cases of gastric carcinoma observed at the Mayo Clinic from 1907 to 1938. While this material is of inestimable value, it could well have been presented in a volume much reduced in length.

Most valuable is the section (the last two chapters and the appendix) by Dr. Joseph Berkson containing the biometric analysis of the data. The reviewer was impressed with the fact that in the 10,890 cases studied, 99 per cent of the patients who survived were traced over a five year period and 98 per cent of the patients who survived were traced over a twenty year period. The correction of the data for the normal survival rate of the population at large makes the interpretation of the results of the observation of the population sample represented in the study much more accurate.

Of the 10,890 cases studied, the carcinomas in 43 per cent were considered to be inoperable. In the remaining 57 per cent the patients were subjected to surgical procedures as follows: Palliative procedures were instituted in 10 per cent; exploratory laparotomies only were done in 22 per cent, and resection was done in the remaining 25 per cent. The calculated mean survival rate for the group was two and two-tenths years. Twenty pages devoted to the mechanics of operating room technic and enumeration of the duties of the operating room nurses before and after their breakfast might well have been omitted. The 50 pages devoted to anesthesia might have been more properly included in some other textbook.

The chapter by Snell on the physiologic considerations of the problems arising in patients with gastric carcinoma is excellent. Of especial interest is the portion of the chapter dealing with vitamin-deficient states observed in these patients.

The chapter by MacCarthy on surgical pathology is likewise of interest, and the discussion of the metastatic spread of gastric carcinoma is well carried out. Desjardins presents an excellent discussion of the problems and procedures involved in the roentgen treatment of gastric carcinoma.

Autonomic Regulations. By Ernst Gellhorn, M.D. Price, $5.50. Pp. 373, with 80 illustrations. New York: Interscience Publishers, Inc., 1943.

This is a highly technical book which sums up a large amount of research on the way in which autonomic centers, particularly in the hypothalamic region, affect many of the automatic functions of the body. Much of the work has been done by Dr. Gellhorn, but he also cites one thousand, one hundred papers by investigators in this field. Subjects discussed are adjustment reactions to changes in the carbon dioxide content of the blood and to anoxia, asphyxia, hemorrhage and hypoglycemia. There are chapters on the autonomic regulation of the cerebral circulation, on the hormones of the hypophysis and on the sympatheticoadrenal and the vago-insulin systems. There are chapters on the roles of the sympathetic, parasympathetic and somatic nervous systems in regulating several of the involuntary functions of the body. Chapter 13 is on reflexes from the carotid sinus; chapter 14 discusses the autonomic basis of emotion; chapter 18 is on the adjustment reactions during general and spinal anesthesia, and chapter 19 deals with what has been learned about changes in the behavior of the autonomic nervous system in patients suffering from schizophrenia.

The book will be of particular value to the student who wishes to find out how the sympathetic and parasympathetic systems of nerves are behaving during a number of situations when the body is under severe strain.

Manual of Oxygen Therapy Techniques. By Albert H. Andrews Jr. Pp. 181, with 16 tables and 33 figures. Chicago: The Year Book Publishers, Inc., 1943.

This handy little manual takes up in minutest detail all technical matters of oxygen therapy including the use of carbon dioxide, helium and water vapor. There are diagrams and photographs of oxygen tents, face masks and other apparatus and exact instructions for the care and use of all this equipment. The book should be useful to every one but especially to house officers and nurses.

Chronic Pulmonary Disease in South Wales Coalminers. I. Medical Studies. Report by the Committee on Industrial Pulmonary Disease. Medical Survey, by P. D'Arcy Hart and E. A. Aslett, with contributions by D. Hicks and R. Yates. Pathological Report by T. H. Belt, with assistance from A. A. Ferris. Price, 10s, 6d. Pp. 222. London: His Majesty's Stationery Office, 1942.

This report on the occurrence and nature of pneumoconiosis in coal miners is the result of a study begun in 1937 and carried through despite the exigencies of war. Its appearance at this time can be credited to the British quality of seeing a job through, while its tremendous thoroughness and its scientific caution in drawing conclusions must be credited to the able collaborators who made and wrote up the medical survey and the pathologic report. The incidence of pneumoconiosis is studied in relation to mining conditions, the type of coal mined, the kind and the duration of work done, the incidence of tuberculous infection and the degree of disability. A prenodular stage of reticulation is described both roentgenologically and pathologically. The illustrations of roentgen changes, showing both whole chests and detailed enlargements of limited areas, are extraordinarily good. There is an excellent bibliography. In addition to those persons with a special interest in silicosis, physicians and roentgenologists in all coal mining regions will find in this report a rich seam well worth digging.

Medical Progress. Edited by Robert N. Nye. Price, $5. Pp. 675. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

Every one who looks through current journals must be impressed with the value of the review articles which appear in the *New England Journal of Medicine*. It is extremely convenient, therefore, to find under one cover the entire series of articles for 1941. It is not possible to review the material in detail, but the authoritative character of the articles is illustrated by such names as Fulton, on aviation medicine; Weiss, on arteritis; Janeway, on bacteriologic matters; Joslin, on diabetes, and Aub, on endocrine glands. The makeup of this book of 675 pages is attractive, and there is an index.

Shock: Its Dynamics, Occurrence and Management. By Virgil H. Moon, Professor of Pathology, Jefferson Medical College, Philadelphia. Price, $4.50, cloth. Pp. 324, with 36 illustrations. Philadelphia: Lea & Febiger, 1942.

The subject material presented in this book is a continuation of and somewhat dependent on the material presented in a previous book by the author (Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938).

The book is divided into two parts. The first part deals with the vascular dynamics of shock, while the second part discusses the prevention, recognition and management of shock. There is a pertinent summary at the conclusion of each chapter. The book contains an adequate number of suitable illustrations. The list of references appended cites many of the important contributions to the subject but is incomplete. The type and the format are excellent and make for easy reading.

The author shows a broader knowledge of the subject in this volume than in his first book and exhibits less bias for one particular theory of the cause of shock. The book is well written. The material included in it is presented in a satisfactory manner but is lacking as a comprehensive discussion of the subject. In view of the fact that the book is apparently not intended as a presentation of the subject in a complete manner, the discussion of terminal pneumonia, extrarenal uremia, status lymphaticus and similar subjects would appear to be of questionable value. On the whole, the book is a worthy contribution to the subject.

A Short History of Cardiology. By James B. Herrick, M.D., Emeritus Professor of Medicine, Rush Medical College. Price, $3.50. Pp. XVI + 258, with 48 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

Dr. Herrick is a rare person, able on passing his eightieth birthday to be regarded by his friends (and they include almost all members of the medical profession) as a man not 80 years old but 80 years young: still young enough to speak and write picturesquely and even to indulge in such a youthful misdemeanor as an attack of acute appendicitis. During his medical career he has stored away a vast fund of medical lore, and in this volume he describes his own concept of the essential history of cardiology during the last three centuries.

Such a book, coming from a man of Dr. Herrick's skill as a medical author and his direct way of looking at things, is bound to be significant. He expresses himself with characteristic style, kindly, gaily, wittily and always in a clear and scholarly manner. The size and the shape of the volume are attractive. It can be slipped into one's pocket readily, to be enjoyed in trains or on holidays in the country or at odd moments when medical history seems most easily perused. The illustrations make up an important feature of the publication. The original drawings or photographs from which the cuts were made have been borrowed for the occasion from the collections of certain of Dr. Herrick's cardiologic intimates, who must be pleased to have their treasures exhibited so handsomely.

Now any disciple of Aesculapius can go on a personally conducted tour through the history of heart disease with Dr. Herrick as guide. The trip is worth taking. It is a privilege to be introduced to worthies like Heberden, Parry, Stokes and the rest of the long line of equally distinguished cardiologists by a person who seems to know them all so affectionately and who, indeed, is himself an important member of their brotherhood.